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Solid organ transplant recipients are required to take anti-rejection drugs for the life of the graft. During the first two years post-transplant, the average drug regimen of a transplant recipient consists of ≥10 items including immunosuppressants, anti-diabetes drugs, anti-hypertensives, and prophylactic anti-infective agents. Because of immunosuppression, transplant recipients are prone to viral and fungal infections and must occasionally undergo a course of anti-infective therapy. Thus, due to the number of medications and the complexity of the drug regimen, the potential for drug interactions is much greater for the transplant recipient than in the average patient population. Although the vast majority of drug interactions are clinically insignificant, a number of interactions are highly significant and can have serious consequences. Therefore, it is imperative for physicians to gain an understanding of the general mechanisms underlying drug interactions and the basic principles involved in the prevention and management of the associated complications. In this article, I will outline these central concepts and review the major immunosuppressants, highlighting the most significant interactions involving each of them.

ABBREVIATIONS:

3A4	CYP3A4 (Cytochrome P450 3A4)
ACE	Angiotensin Converting Enzyme
AUC	Area Under the concentration-vs-time Curve = exposure
BSA	Body Surface Area
CSA	Cyclosporine A
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HMG CoA	3-hydroxy-3-methylglutary-coenzyme A
kD	kilo-Daltons
MDR	Multi-drug Resistant
MMF	Mycophenolate Mofetil
MPA	Mycophenolic Acid
MPAG	Mycophenolic Acid Glucuronide
P-PG	P-glycoprotein
PK	Pharmacokinetic
PD	Pharmacodynamics

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Solid organ transplant recipients are required to take anti-rejection drugs for the life of the graft. In addition, their medication list often includes several other drugs prescribed for therapeutic objectives that may not be directly related to the allograft. During the first two years post-transplant, the average drug regimen of a transplant recipient consists of ≥10 items including immunosuppressants, anti-diabetes drugs, antihypertensives, and prophylactic anti-infective agents. Also, because of immunosuppression, transplant recipients are prone to viral and fungal infections and must occasionally undergo a course of anti-infective therapy. Thus, due to the number of medications and the complexity of the drug regimen, the potential for drug interactions is much greater for the transplant recipient than in the average patient population.

The vast majority of drug interactions are clinically insignificant and some interactions may even be exploited to the patient's benefit.[1,2] A number of interactions, however, are considered to be highly significant and can have serious consequences including graft loss and death. Thus, when the addition or discontinuation of a drug is considered, it is good clinical practice to conduct a systematic review of the patient's entire "medication profile" including over-the-counter medications, herbs and dietary supplements, searching for potentially significant drug interactions.

It is imperative for physicians to gain an understanding of the general mechanisms underlying drug interactions and the basic principles involved in the prevention and management of the associated complications. In this article, I will outline these central concepts and, in the process, review the major immunosuppressants, highlighting the most significant interactions involving each of them.

General Concepts

A drug interaction occurs when a drug, an herb, or a nutritional supplement alters the nature, the magnitude or the duration of the pharmacologic effect of another drug.[1] A clinically significant drug interaction is one that markedly changes the efficacy and/or safety profile of one or both interacting agents.

Drug interactions occur by a variety of mechanisms, which may be divided into two broad categories: pharmacodynamic (PD) and pharmacokinetic (PK).

However, the distinction between PK and PD interactions can be artificial since many of the interactions usually classified as pharmacodynamic have a pharmacokinetic basis. A third category of pharmaceutical interactions occurs when chemically or physically incompatible drugs are mixed in vitro (in a bag, glass bottle, or an infusion line). These will not be discussed here.

Pharmacodynamic (PD) Drug Interactions. A pharmacodynamic (PD) interaction occurs when one drug potentiates or diminishes the pharmacologic effects of another without affecting its kinetics (i.e., without altering its blood level profile). The interaction may occur at the level of the same drug receptor or through the effect of the two agents on the same or on related physiological systems. Examples of PD interactions are provided by:

1. Mycophenolate (MMF) with metoclopramide (exacerbation of diarrhea).
2. Calcineurin inhibitors (cyclosporine or tacrolimus) with other potentially nephrotoxic drugs such as aminoglycosides, amphotericin B, cisplatin, etc.
3. Azathioprine, mycophenolate, or sirolimus with ganciclovir (myelosuppression).

Using a broad definition of what constitutes a pharmacodynamic interaction, it is clear that most of the commonly used combinations of antihypertensive, anti-diabetes, antimicrobial, and immunosuppressive agents are examples of pharmacodynamic interactions utilized to improve therapeutic outcomes.

Pharmacokinetic (PK) Drug Interactions. A pharmacokinetic interaction takes place when one drug alters the adsorption, distribution, metabolism, or excretion of another drug, changing its bioavailability and/or clearance rate. Most PK interactions alter the blood concentration profile of the affected drug. This may be accompanied by significant changes in the drug level at the action site and, consequently, in the final pharmacologic response.

Changes in oral bioavailability may be due to alterations in net absorption or in the pre-systemic drug metabolism, the so-called "first pass" effect. A decrease in net absorption may result from chelation or complex formation in the lumen of the gastrointestinal (GI) tract.[3] For example, cholestyramine and Mg/Al antacids have been shown to reduce mycophenolate bioavailability by approximately 40% and 20% respectively.[4,5] If the offending agent can not be avoided, it must be administered at least two hours after the critical drug (e.g., mycophenolate). Adsorption on the surface of such material as kaolin-pectin or charcoal is another mechanism by which drug absorption can be greatly reduced, leading to treatment failure.[6] These agents should be avoided in transplant patients.

The rate of absorption of an immunosuppressant can be greatly influenced by conditions or drugs that affect GI motility such as anticholinergic agents (e.g., propantheline) or the prokinetic agents metoclopramide and cisapride. In general, since most absorption takes place in the small intestine, a faster gastric emptying leads to a more rapid drug absorption and a higher peak blood concentration. In some cases, an increase in GI motility can enhance not only the rate but also the extent of drug absorption.

P-Glycoprotein (P-GP). For some immunosuppressants, intestinal absorption and tissue distribution are determined in part by the activity of a membrane transporter known as the P-glycoprotein (P-GP) or multi-drug resistance (MDR) protein.[7-9] It is a large (170 kD) protein molecule, a member of a superfamily of membrane transporters known as ABC (ATP-binding cassette). It functions as an ATP-dependent efflux pump transporting a wide range of structurally diverse substances out of the cell interior. The P-GP substrates are generally large, hydrophobic, and electrically neutral or positively charged molecules, and they include cyclosporine, sirolimus, and tacrolimus (see Table 1). Known inhibitors of P-GP include cyclosporine, erythromycin, diltiazem, ketoconazole, midazolam, and verapamil, whereas grapefruit juice and St. John's Wort are suspected potent activators/inducers.[10-12]

Human P-GP is encoded by the MDR-1 gene and expressed in the apical (luminal) membranes of the gastrointestinal tract, proximal tubules, and biliary canaliculi, and in the endothelial cells of the blood-brain and blood-testis barriers.[13] Based on its strategic location at the ingress points in epithelia and blood-tissue barriers, the postulated physiological function of the P-GP is that of a "cellular bouncer" that protects the cell by preventing the entry of harmful xenobiotics. A byproduct of P-GP function is that therapeutic agents may be prevented from reaching their target sites in sufficient concentrations to accomplish the desired therapeutic objective. Elevated P-GP activity is responsible for broad-spectrum, multi-drug resistance (MDR) in

Table 1 | **SUBSTRATES, INHIBITORS AND ACTIVATORS/INDUCERS OF THE P-GLYCOPROTEIN**

SUBSTRATES
Antineoplastic agents: Doxorubicin, etoposide, paclitaxil, and vinca alkaloids
Azole antifungals: Itraconazole and ketoconazole
Calcium antagonists: Diltiazem and verapamil
Anti-arrhythmics: Amiodarone, lidocaine, quinidine
HIV protease inhibitors: Indinavir, nelfinavir, ritonavir, saquinavir
Immunosuppressants: Cyclosporine, tacrolimus, and sirolimus
Steroids and related compounds: Steroid hormones; dexamethasone; bile acids
Miscellaneous: Colchicine, digoxin, erythromycin, loperamide, ondansetron, etc
*Notice that many of these drugs are also substrates for the cytochrome P450 enzyme system.
INHIBITORS
Cyclosporine
Diltiazem
Erythromycin
Ketoconazole
Midazolam
Tacrolimus
Verapamil
ACTIVATORS/INDUCERS
Grapefruit juice
St. John's Wort
Chronic tissue exposure to P-GP substrates (e.g., cyclosporine) is thought to increase its expression (upregulation) in cell membranes.

tumors and may also play a role in the development of steroid-resistant acute allograft rejection.[14,15]

The P-GP activity can be an important determinant of net transport of immunosuppressive drugs across the gastrointestinal epithelium. Differences among patients in the expression of P-GP in the intestinal apical cell membrane may explain in part the wide inter-individual variability in the absorption of these drugs.[7] More importantly, drugs that modulate P-GP activity can have a significant impact on the kinetics of immunosuppressants. The increase in the oral bioavailability of cyclosporine secondary to the coadministration of agents such as ketoconazole is in part attributable to the inhibition of P-GP and associated increase in drug absorption.[16-19] However, the inhibition of cytochrome P450 (see below) probably accounts for a greater portion of this effect.

Cyclosporine is both a substrate and a modulator of P-GP. It is an effective inhibitor when co-administered with other P-GP substrates, which may lead to significant interactions. Inhibition of P-GP may contribute significantly to the rise in the sirolimus blood level when the two drugs are given together.[20-22] Cyclosporine can also interfere with P-GP mediated elimination of certain drugs in the urine[23] or in the bile (e.g., colchicine).[24] A serious case of acute myopathy attributed to colchicine accumulation has recently been reported in a heart transplant recipient maintained on cyclosporine.[25]

Drug Interactions Involving Changes in Drug Metabolism—The Cytochrome P450 (CYP). Interactions involving altered drug metabolism are the most common type and often involve the cytochrome P450 enzyme system (CYP450), a complex set of heme containing enzymes with varying degrees of structural homology.[28] Human CYP450 proteins are found in the membranes of the endoplasmic reticulum, mainly in the liver, with smaller amounts in the small intestine, kidneys, lungs and brain.

The CYP450 system consists of over 50 individual isozymes (or isoforms) (Table 2). This so-called superfamily of enzymes is subdivided into families and subfamilies. Of all the CYP450 isoforms, the 3A4 is perhaps the most important for the metabolism of immunosuppressive agents. The three major immunosuppressive drugs—cyclosporine, sirolimus and tacrolimus—are metabolized primarily by the 3A4 isoform. All three drugs undergo relatively extensive and variable 3A4-mediated first-pass (presystemic) metabolism. Therefore, agents that modify the 3A4 activity through competitive or non-competitive inhibition or through enhanced expression (upregulation or induction), will have a significant impact on the kinetics of the CYP3A4 substrates.

Table 2 | **IMPORTANT CYTOCHROME P450 ISOFORMS AND SELECTED SUBSTRATES**

1A2 (13%)[a]	Clozapine, cyclobenzaprine (Flexeril); naproxen; phenacetin; reluzole; tacrine; theophylline [Inhibitors: cimetidine, fluoquinolones; fluvoxamine; ticlodipine]
2B6 (0.1-20%)[a]	Cyclophosphamide; 3-mephenytoin; nevirapine [Inhibitors: ketoconazole (?)]
2C9 (15%)[a]	NSAIDs (celecoxib, diclofenac, ibuprofen, indomethacin, piroxicam); Fluvastatin; glipizide; losartan; irbesartan (not valsartan or candesartan); phenytoin; sulfamethoxazole; tamoxifen; tolbutamide; torsemide; S-warfarin [Inhibitors: amiodarone; fluconazole; hyperforin[b], isoniazid, miconazole, sulfamethoxazole, ticlodipine]
2C19 (3%)[a]	Amitriptyline; citalopram; clomipramine; cyclophosphamide; diazepam; S-mephenytoin; lansoprazole; omeprazole; pantoprazole; proguanil [Inhibitors: fluconazole, fluoxetine, fluvoxamine, ketoconazole, lansoprazole, omeprazole, ticlodipine]
2D6 (1.5%)[a]	Codeine; despiramine; dextromethorphan; encainide; flecainide; haloperidol; metoprolol; mexiletine; nortriptyline; ondansetron; paroxetine; propafenone; thioridazine; timolol; tramadol; venlafaxine (Effexor®) [Inhibitors: amiodarone, cimetidine, cisapride, clomipramine, chlorpheniramine, diphenhydramine (Benadryl®), fluoxetine, haloperidol, hyperforin[b], methadone, paroxetine, quinidine, ritonavir, terbinafine]
2E1 (7%)[a]	Acetaminophen; chlorzoxazone; dapsone; ethanol; halothane [Inhibitors: disulfiram]
3A4 (29%)[a]	Anti-arrhythmic drugs: Amiodarone; lidocaine; quinidine Antiviral agents: Amprenavir; indinavir; nelfinavir; ritonavir; saquinavir; Antidepressants: buspirone; citalopram (Celexa®); fluoxetine (Prozac®); fluvoxamine; nefazodone (Serzone®); sertraline (Zoloft®); trazodone; Benzodiazepines: Alprazolam; diazepam; midazolam; triazolam Ca Channel Blockers: Diltiazem; felodipine; isradipine; nicardipine; nifedipine; nisoldipine; verapamil Chemotherapeutic agents: Etoposide; ifosfamide; tamoxifen; vinblastine; vincristine. H_1-antagonists: Astemizole; chlorpheniramine; loratidine; terfenadine. HMG CoA reductase inhibitors (statins): atorvastatin; cerivastatin; lovastatin; simvastatin; (not pravastatin or fluvastatin) Immunosuppressants: CSA; tacrolimus; sirolimus Macrolide antibiotics: Erythromycin and clarithromycin (not azithromycin) Opioids: Alfantanil; fentanyl; sufantanil; methadone. Others: haloperidol; pimozide; quinine; sildenafil [Inhibitors: see Table 3]

[a]Percent of the immunoquantified level of human hepatic CYP450; [b]Hyperforin is the putative active constituent of St. John's Wort.

Inhibition of CYP3A4 and the accompanying reduction in presystemic metabolism increases the level of exposure of the body to the drug, which can be measured as the area under the concentration-versus-time curve (AUC). This effect (i.e., increased bioavailability) can be further augmented by also inhibiting the efflux pump (P-GP). Many of the inhibitors of CYP3A4 inhibit P-GP as well, and cause a significant increase in immunosuppressant exposure.

Inhibition of the CYP3A4. Inhibition of 3A4, as a result of the co-administration of potent inhibitors like ketoconazole and nefazodone,[29,30] can cause profound exacerbation of the dose-related adverse effects associated with immunosuppressants. A marked rise in the blood level of cyclosporine or tacrolimus is associated with telltale signs such as nephrotoxicity, hypertension, headache and neurological symptoms including tremor, and less frequently, confusion, agitation, delirium, expressive aphasia and seizures. These neurological problems may be related to the inhibition of the P-glycoprotein efflux pump in the blood-brain barrier allowing higher levels of the immunosuppressant to occur in brain tissue.[31]

Among the well documented inhibitors of 3A4 are:

1. Azole antifungal agents, especially ketoconazole and itraconazole;[32]
2. Macrolide antibiotics (erythromycin and clarithromycin);[33,34]
3. Grapefruit juice (see below)
4. Non-dihydropyridine calcium antagonists (diltiazem and verapamil);
5. Dihydropyridine class of calcium channel blockers (nicardipine and nifedipine) except for amlodipine, which appears to possess little or no effect on CYP3A4.[35]

Other clinically relevant inhibitors are listed in Table 3.

The CYP3A4 inhibitors vary in terms of the mechanism and the degree of inhibition. In vitro studies suggest that ketoconazole is about 10 times more potent than itraconazole and 400 times more than fluconazole.[30,32] In adult patients, fluconazole doses <200 mg per day have little or no effect on cyclosporine (or tacrolimus) trough levels.[30,36] However, in children, a 100 mg dose of fluconazole has been successfully used to reduce the tacrolimus dose required to maintain an adequate trough level.[37]

Table 3 | **INHIBITORS OF CYP450 3A4** [■ Denotes a particularly strong inhibitor. However, all the inhibitors listed below are clinically significant.]

MACROLIDES AND RELATED COMPOUNDS[1]
■ Clarithromycin
Cyclosporine
■ Erythromycin
■ Troleandomycin
■ Synercid® (quinupristin + dalfopristin, 30:70 ratio)
AZOLE ANTIFUNGAL AGENTS[30]
■ Ketoconazole
■ Itraconazole
Clotrimazole
Fluconazole
Miconazole
ANTIDEPRESSANTS
Fluoxetine (Prozac®)
Fluvoxamine (Luvox®)
Citalopram
■ Nefazodone (Serzone®)
CA CHANNEL BLOCKERS
■ Diltiazem
■ Verapamil
Dihydropyridines
Felodipine
Nicardipine
Nifedipine
HIV DRUGS (PROTEASE INHIBITORS)[47]
■ Delaviridine
Amprenavir
Indinavir
Nelfinavir
■ Ritonavir
Saquinavir
OTHERS
Amiodarone
■ Cimetidine
■ Grapefruit juice
Hyperforin[a]

[a]Hyperforin is the putative active (antidepressant) constituent of St. John's Wort.

In renal transplant recipients, ketoconazole reduces the required daily oral dose of cyclosporine by more than 80%. This cyclosporine-sparing effect of ketoconazole has been exploited in many transplant centers for its apparent pharmacoeconomic benefit.[38,39] However, it should be noted that ketoconazole and similar agents alter not only the bioavailability and clearance of the calcineurin inhibitor, but also its tissue distribution. Such a change can have a significant effect on the safety profile of the immunosuppressive drug.

Grapefruit juice. Grapefruit juice has been shown to increase the bioavailability and reduce the metabolic clearance of many drugs including immunosuppressants. Other drugs affected by grapefruit include calcium antagonists, HMG-CoA reductase inhibitors (statins), H1-blockers (antihistamines), benzodiazepines, and HIV protease inhibitors.[40,41] Generally, a drug that carries a warning of possible interactions with the macrolide antibiotics and/or azole antifungal agents is likely to interact also with grapefruit.

Table 4 | **INDUCERS OF CYP450 3A4** Bolded items denote particularly strong agents. However, all the inducers listed below are clinically significant.

Carbamazepine
Dexamethasone
Phenobarbital
Phenytoin
St. John's Wort (chronic use)
Rifampin
Rifabutin
Efavirenz
Nevirapine
Nafcillin
Clindamycin

The Grapefruit effect is mediated by selective post-translational downregulation of CYP3A4 expression leading to reduced CYP3A4 activity in enterocytes. This leads to a reduction in intestinal pre-systemic drug metabolism and enhanced oral bioavailability of drugs that are substrates for the CYP3A4 isoform. Grapefruit also inhibits hepatic drug metabolism, further increasing drug bioavailability, and reducing drug clearance. These effects promote drug accumulation and enhance the risk of drug toxicity. Furanocoumarins (e.g., bergamottin) and flavonoids (e.g., naringin and naringenin) are the grapefruit constituents thought to be responsible for the inhibition of CYP3A4. These substances are apparently not found in other fruits such as orange, dark grape, mango, peach, and passion fruit.[42]

Grapefruit juice increases cyclosporine bioavailability by approximately 60%, which encouraged some clinicians and patients to use it to reduce cyclosporine dose and medication expense. However, the inconsistent amounts of active ingredients in grapefruit juice from brand to brand and from lot to lot make it an unreliable adjunct agent in immunosuppressive therapy. Using grapefruit juice will not only endanger the graft, it will also expose the patient to serious drug toxicities involving both immunosuppressive and non-immunosuppressive drugs such as antihypertensive and lipid-lowering agents (see below). In addition, grapefruit juice is an activator/inducer of the P-GP.[10] Therefore, chronic consumption of grapefruit can reduce the bioavailabilities of drugs that are not substrates for the CYP3A4 and may lead to treatment failures.

Drug Interactions that Can Cause Rhabdomyolysis. Myositis and rhabdomyolysis have been reported in patients treated with cyclosporine in combination with the lipid-lowering HMG-CoA reductase inhibitors (statins).[1] Documented cases of rhabdomyolysis have been reported for all the statins that are metabolized primarily by the CYP3A4—lovastatin, simvastatin, cerivastatin, and atorvastatin.[1,43-46] In contrast, fluvastatin (metabolized mainly by CYP2C9) and pravastatin (eliminated by other metabolic routes) are less likely to be involved in this type of interaction. Nevertheless, a 5-fold increase in pravastatin bioavailability has been reported in the presence of cyclosporine.[1,43] The mechanism for the increase in the bioavailability of pravastatin is unclear, but it may be due to the cyclosporine-mediated inhibition of P-GP.

Rhabdomyolysis has also been reported following the addition of itraconazole (200 mg daily) to the drug regimens of patients who were stable on a lipid-lowering therapy with lovastatin or simvastatin. This was associated with marked (10- to 25-fold) increases in the bioavailability and peak statin level.[30] Similar complications can occur when a statin (particularly lovastatin or simvastatin) is combined with any effective CYP3A4 inhibitor (erythromycin, grapefruit, diltiazem, verapamil, etc.).[1]

Induction of the CYP3A4. Enhanced expression (induction) of CYP3A4 can cause a several-fold elevation in both intestinal and hepatic drug metabolism. The combined effects of reduced bioavailability and enhanced clearance can lead to a sharp drop in the blood level of an immunosuppressant, which may trigger acute allograft rejection or allograft loss. Potent inducers of the CYP3A4 isoform (Table 4) include carbamazepine, phenobarbital, phenytoin, rifampin, rifabutin, and the extract of St. John's Wort.[12,48,49] There are many reports in the literature describing serious interactions in transplant patients involving these agents and cyclosporine or tacrolimus.[2,50,51]

Although the effect of the addition of an inducer to the drug regimen of a transplant patient may be noticeable within 24-48 hours, the full impact may require a week or more to be manifest. Similarly, when an enzyme inducer is discontinued, it may take more than a week for the CYP3A4 activity to

Table 5 | **IMPORTANT AND POTENTIALLY SIGNIFICANT DRUG INTERACTIONS INVOLVING CYCLOSPORINE, TACROLIMUS AND SIROLIMUS** [CSA = cyclosporine A; CYP3A4 = cytochrome P450 3A4 isoform]

■ denotes an important interaction that should be prevented or taken into account, requiring close monitoring.

DRUG OR DRUG CLASS	EFFECTS AND MECHANISMS OF INTERACTION
Acetazolamide	PD interaction: hyperchloremic metabolic acidosis
ACE Inhibitors	PD interactions; hyperkalemia and reduced GFR (use with caution)
■ Acyclovir	•PD interaction: increased risk of nephrotoxicity •Increased risk of neurotoxicity (with CSA or tacrolimus)
Amikacin	See Nephrotoxic Drugs
Amiloride	⇒ ↓ renal K^+ secretion ⇒ hyperkalemia
Amiodarone	See CYP3A4 inhibitors
Amphotericin B	See Nephrotoxic Drugs
Antacids	⇒ ↓ absorption of immunosuppressants (particularly mycophenolate)
■ Anticonvulsants	See CYP3A4 inducers
Altorvastatin	See Statins
β-blockers	⇒ ↑ efflux of cell K^+ ⇒ ↑ hyperkalemia (demonstrated with CSA + β-blockers)
Bromocriptine	See CYP3A4 inhibitors
■ Carbamazepine	⇒ CYP3A4 induction ⇒ ↑ metabolism (CSA, Tacro, Siro) ⇒ ↓ level
Captopril	See ACE Inhibitors
Carvedilol[58]	⇒ small reduction in CSA clearance leading to a 20% dose reduction. Carvedilol is metabolized primarily by 2D6 and 2C9 with only a minor contribution by 3A4. • See also β-blockers above
Cerivastatin	See Statins
Chloroquine	See CYP3A4 inhibitors
■ Cholestyramine	⇒ ↓ drug absorption
■ Chloramphenicol[59, 60]	See CYP3A4 inhibitors
■ Cimetidine	See CYP3A4 inhibitors (cimetidine is a nonspecific inhibitor of the P450)
Ciprofloxacin	• PD interaction with CSA. Cipro may reduce the inhibitory effect of CSA on IL-2 production reducing the immunosuppressive effect. • No evidence of PK interaction with CSA, tacrolimus or sirolimus.
■ Cisapride	⇒ ↑ GI motility and gastric emptying ⇒ ↑ absorption rate ⇒ ↑ level
■ Clarithromycin	See CYP3A4 inhibitors
Clindamycin[61]	⇒ ↑ clearance of CSA ⇒ ↓ level [minor interaction; monitor]
Clotrimazole	See CYP3A4 inhibitors
Colchicine[24]	• ⇒ competitive inhibition of P-GP ⇒ ↑ penetration of CSA (tacrolimus?) through the blood brain barrier ⇒ ↑ neurotoxicity • CSA inhibits colchicine transport into bile ⇒ ↑ colchicine level ⇒ acute myopathy. Use with caution.
Co-trimoxazole[62]	• May exacerbate the hyperkalemia induced by tacrolimus or CSA • May exacerbate the neutropenia induced by mycophenolate, azathioprine, or ganciclovir
■ Cyclosporine	⇒ ↑ bioavailability of sirolimus (possibly due to P-GP inhibition and competition for CYP3A4). Bioavailability is up 30-40% when the two drugs are separated by 4 hrs and >100% when administered together at the same time.
■ CYP3A4 inducers	⇒ ↑ expression of CYP450 ⇒ ↑3A4 enzyme activity ⇒ ↑oxidative metabolism ⇒ ↓ bioavailability & ↑clearance ⇒ ⇓ blood level of immunosuppressant ⇒ ↑ risk of acute allograft rejection. Affected immunosuppressants: CSA, tacrolimus and sirolimus.

return to its baseline level. Therefore, closer monitoring and more frequent dose adjustment may be necessary during the transition (onset or offset) period.

Interactions Involving Specific Immunosuppressants

The clinical pharmacology, especially the pharmacokinetics, of cyclosporine, tacrolimus, mycophenolate, and sirolimus is complex and unpredictable. Characteristics of the kinetics of these agents include a relatively low therapeutic index unique to each patient, and a variable rate and extent of net absorption, metabolism, and elimination. Therefore, individually optimized immunosuppressive therapy is necessary. The potential for multiple drug interactions can further complicate this task. The following is a brief account of the main drug interactions involving azathioprine, cyclosporine, mycophenolate, sirolimus, and tacrolimus. A brief description of the drug, its

Table 5 | **Important and Potentially Significant Drug Interactions Involving Cyclosporine, Tacrolimus and Sirolimus (cont.)** [CSA = cyclosporine A; CYP3A4 = cytochrome P450 3A4 isoform]

■ denotes an important interaction that should be prevented or taken into account, requiring close monitoring.

Drug or Drug Class	Effects and Mechanisms of Interaction
■ **CYP3A4 inhibitors**	⇒ ↓ metabolism ⇒ ↑ bioavailability + ↓ clearance ⇒ ⇑ blood level of CSA, tacrolimus, and sirolimus ⇒ ↑ risk of toxicity (nephrotoxicity, neurotoxicity, myelosuppression, etc) and excessive immunosuppression (⇒ infections and post-transplant lymphoproliferative disorders).
Dexamethasone	See CYP3A4 inducers
Digoxin	• CSA may inhibit the renal excretion of digoxin (via the P-GP) ⇒ ↑ digoxin level • PD interaction (cardiac digoxin toxicity) is possible due to tacrolimus-induced hyperkalemia and hypomagnesemia • Digoxin may increase CSA bioavailability by 15–20%[63]
Danazol[2]	See CYP3A4 inhibitors
Dapsone[59]	See CYP3A4 inhibitors (minor interaction)
■ Diltiazem	See CYP3A4 inhibitors
■ Efavirenz	See CYP3A4 inducers
Enalapril	See ACE Inhibitors
Ergotamine[64]	See CYP3A4 inhibitors (minor interaction)
■ Erythromycin	See CYP3A4 inhibitors
■ Fluconazole	See CYP3A4 inhibitors
■ Fluoxetine	See CYP3A4 inhibitors
■ Fluvoxamine	See CYP3A4 inhibitors
■ Foscarnet	See Nephrotoxic Drugs
Fosinopril	See ACE Inhibitors
■ Fosphenytoin	See CYP3A4 inducers
Ganciclovir	• PD interaction: ↑ risk of nephrotoxicity (with CSA or tacrolimus) • PD interaction: ↑ risk of myelosuppression (azathioprine, MMF, or sirolimus)
Gentamicin	See Nephrotoxic Drugs
■ Grapefruit Juice	See CYP3A4 inhibitors
■ Hypericum perforatum	See CYP3A4 inducers (chronic use)
■ Itraconazole	See CYP3A4 inhibitors
■ Ketoconazole	See CYP3A4 inhibitors
■ Lovastatin	See Statins
Mefloquine[59]	See CYP3A4 inhibitors (minor interaction)
Methylprednisolone	• PD interaction: ↑ immunosuppression • Tacrolimus reduces steroid metabolism (steroid-sparing effect of tacrolimus)
Metoclopramide	⇒ ↑ GI motility and gastric emptying ⇒ ↑ absorption rate ⇒ ↑ peak level
Metronidazole[6,65]	• See CYP3A4 inhibitors • ↓ bacterial glucuronidase ⇒ ↓ enterohepatic cycling of MPA ⇒ ↓ MPA level.
■ Miconazole	See CYP3A4 inhibitors
Midazolam	See CYP3A4 inhibitors
Nafcillin[66]	⇒ ↑ clearance of CSA ⇒ ↓ level [minor interaction; monitor]
■ Nefazodone	See CYP3A4 inhibitors
■ Nelfinavir	See CYP3A4 inhibitors
Nephrotoxic Drugs	⇒ ⇑ risk of nephrotoxicity when used with CSA or tacrolimus
Nevirapine	See CYP3A4 inducers (expected but yet to be reported)

kinetics, and the main adverse effects associate with its use are also included.

Azathioprine. Azathioprine was originally FDA approved in 1968 as an adjunct immunosuppressant for use in renal transplant patients. Prior to the advent of cyclosporine, the combination of azathioprine and corticosteroids (prednisone or prednisolone) was the mainstay of immunosuppressive therapy for solid organ transplantation. However, in recent years the use of azathioprine has largely been supplanted by mycophenolate, a more specific inhibitor of lymphocyte purine metabolism.

Azathioprine is a pro-drug, which is converted in the body via a non-enzymatic reaction to 6-mercaptopurine (6-MP), a purine analog that interferes with nucleotides, thereby inhibiting T-cell proliferation. Azathioprine is a non-specific immunosuppressant whose primary targets are the cells in the bone marrow.

Table 5 **IMPORTANT AND POTENTIALLY SIGNIFICANT DRUG INTERACTIONS INVOLVING CYCLOSPORINE, TACROLIMUS AND SIROLIMUS (CONT.)** [CSA = cyclosporine A; CYP3A4 = cytochrome P450 3A4 isoform]

■ denotes an important interaction that should be prevented or taken into account, requiring close monitoring.

DRUG OR DRUG CLASS	EFFECTS AND MECHANISMS OF INTERACTION
Nicardipine	See CYP3A4 inhibitors
Nifedipine	See CYP3A4 inhibitors
NSAIDs	⇒ ↑ risk of nephrotoxicity
Octreotide	⇒ ↓ absorption ⇒ ↓ level of the immunosuppressant
Omeprazole[64]	See CYP3A4 inhibitors
Oxycodone[63]	⇒ ↓ CSA bioavailability by ~ 15% (mechanism unknown)
Quinidine	See CYP3A4 inhibitors (minor interaction)
Quinine[63]	⇒ ↑ CSA bioavailability by ~25% (mechanism unknown)
Phenobarbital	See CYP3A4 inducers
■ Phenytoin	See CYP3A4 inducers
Probucol[67]	⇒ ↓ CSA bioavailability ⇒ ↓ CSA level (mechanism unknown)
■ Rifabutin	See CYP3A4 inducers
■ Rifampin	See CYP3A4 inducers
■ Ritonavir	See CYP3A4 inhibitors
Rofecoxib (Vioxx®)	See CYP3A4 inducers [Rofecoxib is not a substrate for the CYP450, but it is a mild inducer of the CYP3A4].
■ Saquinavir	See CYP3A4 inhibitors
Sildenafil	May competitively inhibit CYP3A4 leading to increased level of CSA, tacrolimus, and sirolimus. Reported to increase GFR in kidney transplant recipients.
■ Simvastatin	See Statins
Sirolimus[68]	⇒ ↑ CSA bioavailability by ~15% (when separated by 4 hrs)
■ St John's Wort[12]	See CYP3A4 inducers (chronic use)
■ **Statins**[69]	• Atorvastatin, cerivastatin, lovastatin, and simvastatin are all substrates for 3A4 and most of them are subject to extensive pre-systemic drug metabolism. • CSA (and perhaps tacrolimus) ⇒ ↑ bioavailability & ↓ clearance of statins ⇒ accumulation of statins ⇒ ⇑ risk of myositis and rhabdomyolysis • Use lower doses of the statin and monitor for signs of muscle damage.
■ Synercid®	See CYP3A4 inhibitors
Spironolactone	⇒ ↓ renal K^+ secretion ⇒ hyperkalemia
Triamterene	⇒ ↓ renal K^+ secretion ⇒ hyperkalemia
Troglitazone	See CYP3A4 inducers
■ Troleandomycin	See CYP3A4 inhibitors
■ Verapamil	See CYP3A4 inhibitors

The dose of azathioprine is 1-2 mg/kg PO qday. The dose may be limited by the side effects, which can be sufficiently severe to warrant discontinuation of therapy.

Main side effects. Leukopenia, pancytopenia, thrombocytopenia, and/or macrocytic anemia, occur to varying degrees in >50% of patients. Hepatotoxicity occurs in 2-10% of transplant patients receiving azathioprine. A life-threatening condition known as veno-occlusive disease of the liver occurs in <1% of the patients following chronic azathioprine therapy. Nausea and vomiting occur in 10-15% of patients particularly during the first few weeks or months.

Drug interactions. Coadministration with ganciclovir, ACE-inhibitors, carbamazepine, clozapine, or co-trimoxazole can lead to the exacerbation of hematologic toxicity. Allopurinol, an analog of hypoxanthine, is a powerful inhibitor of xanthine oxidase, the enzyme responsible for the inactivation of 6-mercaptopurine (6-MP). The combination of allopurinol and azathioprine leads to accumulation of 6-MP and potentially life-threatening myelosuppression. If allopurinol is absolutely necessary, the azathioprine dose should be immediately reduced by 50-75%.

Cyclosporine A. Cyclosporine A (CSA) is a macrocyclic lactone of fungal origin possessing strong immunosuppressive actions. CSA is indicated for the prophylaxis of allograft rejection for kidney, heart, and liver transplant recipients, and for the prevention of graft-versus-host disease in bone marrow transplants. CSA was the first calcineurin-

inhibiting immunosuppressive agent to be introduced into clinical practice. It achieves its effects on the immune system by inhibiting a phosphatase called calcineurin, which is an enzyme required for the production of interleukin-2 (IL-2). Suppression of IL-2 production impairs the early stages of the activation and proliferation of helper and cytotoxic T cells. In short, cyclosporine works mainly by preventing the activation and proliferation of T cells.

CSA is available in both oral and injectable forms. The oral dose is roughly three times larger than the IV dose. The most commonly used oral preparation (Neoral® or Gengraf®) is referred to as "modified microemulsion" because it contains surfactant material to enhance the consistency of CSA absorption. The oral maintenance dose ranges from 3 to 10 mg/kg/day (usually divided bid). The dose is determined based mainly on an assessment of the overall risk of acute allograft rejection, which is much higher in the early post-transplant period than months or years after the transplant. Also, lower doses of CSA are needed for optimal immunosuppression when CSA is part of a "triple therapy" regimen consisting of steroids, mycophenolate and CSA.

Main side effects. The main side effects include nephrotoxicity, hypertension, hyperkalemia, hypomagnesemia, hyperuricemia and dyslipidemia. Neurotoxicity (tremors, confusion and seizures) may occur in predisposed patients. Long-term use is associated with cosmetic toxicity (hirsutism, gingival hyperplasia and acne). Nausea/vomiting, abdominal pain and diarrhea may also occur transiently. Rare adverse effects include hepatotoxicity, pancreatitis and anaphylaxis.

Pharmacodynamic drug interactions involving cyclosporine. Additive nephrotoxicity can occur if cyclosporine is administered with other nephrotoxic drugs such as amphotericin B, acyclovir, aminoglycosides, foscarnet, co-trimoxazole [Sulfamethoxazole-trimethoprim, (SMX-TMP)] and nonsteroidal anti-inflammatory drugs (NSAIDs). Neurotoxicity (confusion, tremor, agitation and seizures) may be increased when imipenem is administered to CSA-treated patients. Meropenem may be a safer carbapenem for transplant patients receiving either CSA or tacrolimus. Increased risk of hyperkalemia occurs when CSA is combined with K-sparing diuretics such as spironolactone, amiloride and triamterene. Exacerbation of hypomagnesemia occurs when CSA is used with loop diuretics, aminoglycosides, or amphotericin B.

Pharmacokinetic drug interactions involving cyclosporine. Adverse drug reactions associated with high CSA levels (nephrotoxicity, hypertension, tremor, infections, etc.) are likely to be precipitated by the addition of agents that inhibit CSA metabolism. These include ketoconazole, itraconazole, erythromycin, clarithromycin, cimetidine, grapefruit juice, danazol, nefazodone (Serzone®), diltiazem, verapamil and others (see Tables 3 and 5). Increased risk of acute allograft rejection is associated with use of agents that increase CSA metabolism (via CYP3A4 induction), accelerating its clearance and lowering its level (see Tables 4 and 5). For example, cases of cardiac allograft rejection have been reported in patients after several weeks of daily intake of the St. John's Wort extract. Transplant patients must avoid taking phytopharmaceuticals and "dietary" supplements until they are proven safe.

The risk of myopathy (myositis and rhabdomyolysis) is increased when a lipid-lowering drug like lovastatin and simvastatin is added to the drug regimen of a transplant patient maintained on CSA. Apparently the bioavailabilities of statins are markedly increased by the coadministration of CSA. However, it should be emphasized that the risk of rhabdomyolysis is very small and should not discourage physicians from initiating lipid-lowering therapy in transplant patients when indicated. Dosing of lipid-lowering agents and monitoring for adverse effects in the well transplant recipient is discussed in detail by Abtahi and Zand elsewhere in this issue.

CSA and sirolimus share the same CYP450 isoform (3A4) and are both substrates for P-glycoprotein efflux pump. CSA increases sirolimus bioavailability and blood level even when the two drugs are separated by the recommended 4 hours interval. This effect is even more pronounced when the two drugs are given at the same time. Administering the two drugs at the same time can lead to dose-related adverse drug reactions of sirolimus and CSA, including profound immunosuppression. Sirolimus appears to increase the bioavailability and the drug level of cyclosporine. However, these effects appear to be minor compared to the effect of CSA on sirolimus kinetics.

Tropical fruits such as papaya may contain constituents that can inactivate CSA in the gastrointestinal tract. Intake of such fruits should be taken several hours after the cyclosporine dose.

Mycophenolate. Mycophenolate mofetil or MMF (CellCept®) is the ester pro-drug of mycophenolic acid (MPA). MMF is used for immunosuppression in combination with a calcineurin inhibitor plus steroids. MMF is indicated for the prevention of organ rejection in patients receiving allogeneic renal or cardiac transplants, and is also widely used in liver transplant recipients.

MMF is available in injectable and oral forms. The oral and intravenous doses are the same, and the usual adult dose is 1 gram twice daily. For children, the dose is 600 mg per m^2 BSA per dose twice daily, not to exceed 2 grams per day. In the body, MMF is completely hydrolyzed to MPA, the active metabolite. After oral administration to healthy volunteers, MMF is rapidly and almost completely (>90%) absorbed. The conversion of MMF to MPA takes place in the cells of the intestine and the liver, before the drug reaches the systemic circulation. MPA is extensively bound to plasma proteins (~97%), and its volume of distribution is ~4 L/kg. MPA undergoes conjugation mainly in the liver to form the pharmacologically inactive phenolic glucuronide of MPA (MPAG). The elimination half-life of MPA is about 18 hours.

Most of MPAG is eliminated in the urine via tubular secretion and its clearance correlates well with GFR. Severe renal impairment results in the accumulation of MPAG and MPA.[5,52] However, a significant amount of MPAG is secreted into the bile only to be converted back to MPA and returned to the liver (enterohepatic recycling). Enterohepatic recycling is believed to contribute significantly to the MPA serum level. The co-administration of cholestyramine (at 4 g tid) which interferes with the enterohepatic recycling of MPA results in approximately 40% decrease in the MPA AUC.[5,53]

Contraindications and cautions. MMF must be used with caution in patients with severe renal insufficiency due to the retention of MPAG and the accumulation of MPA. The drug should also be used with caution in patients with gastrointestinal disorders (active peptic ulcer, GI bleed, diarrhea, etc.). MMF can cause leukopenia and thrombocytopenia. MMF should not be used in patients with ongoing infections. It also should not be used in women with childbearing potential. Immunization within 2 weeks prior to or during MMF therapy is probably ineffective. Passive immunoprophylaxis with immune globulins may be indicated for immunocompromised patients. Patients receiving MMF and/or other immunosuppressants should not be exposed to others who have recently received live virus vaccines, such as the oral poliovirus vaccine (OPV).

Main side effects. The most frequent side effects of initiating MMF therapy are the gastrointestinal disturbances including abdominal pain, diarrhea, constipation, and nausea/vomiting. These side effects usually occur within 1-2 weeks of initiating therapy or increasing the dose. The hematologic side effects include anemia, leukopenia, thrombocytopenia, or leukocytosis. An increased risk of viral infection also occurs with MMF therapy.

Pharmacodynamic drug interactions involving MMF. Exacerbation of hematologic toxicity (leukopenia, thrombocytopenia) can be additive when other agents with this effect are co-administered with MMF (e.g., acyclovir, ganciclovir, carbamazepine, clozapine, co-trimoxazole)

Pharmacokinetic drug interactions involving MMF. Aluminum or magnesium based antacids and oral Mg supplements reduce MMF absorption by 15-20%. MMF should be administered 2-3 hours before the antacid or supplement.[4] Co-administration of cholestyramine reduces the bioavailability of MMF by ~40%, and should be avoided in transplant patients. The plasma level of drugs that are also substrates of the proximal tubule organic transport system (e.g., acyclovir and ganciclovir) may increase in the presence of MPAG due to competition for tubular secretion. This interaction may be significant in patients with markedly reduced renal function. Similarly, probenecid may increase MPA level (2- to 3-fold) due to competitive inhibition of tubular secretion. The administration of antibiotics such as metronidazole and fluoroquinolones and the resultant elimination of intestinal flora are associated with a 35-45% reduction in MPA bioavailability (AUC).[6] An adjustment in MMF dose may be required when these antibiotics are given to transplant patients.

Sirolimus (Rapamune). Sirolimus is a relatively new macrocyclic immunosuppressive agent of fungal origin. Structurally sirolimus resembles tacrolimus and binds to the same immunophilin, an intracellular protein known as FKBP-12. However, sirolimus has a novel mechanism of action and does not

inhibit calcineurin. Whereas the calcineurin inhibitors (tacrolimus and cyclosporine) block interleukin-2 (IL-2) gene transcription and early activation of the T lymphocytes (transition from G0 to G1 phase of cell cycle), sirolimus inhibits IL-2-mediated signal transduction and the progression of cells from G1 to S phase of the cell cycle. In the cell, sirolimus binds to FKBP-12 and the sirolimus-FKBP-12 complex binds to and inhibits the activation of a specific cell-cycle regulatory kinase known as the mammalian Target Of Rapamycin (mTOR). Inhibition of mTOR suppresses cytokine-driven T-lymphocyte proliferation.[21,56] Sirolimus also interferes with the differentiation of B lymphocytes into antibody-producing (plasma) cells, decreasing the levels of IgM, IgG, and IgA.

Following oral administration, sirolimus is rapidly absorbed with the peak blood level occurring after 1–2 hours. The bioavailability of sirolimus is low (~14%) because of presystemic metabolism and the P-glycoprotein mediated countertransport. Fatty food can significantly increase the extent of sirolimus absorption (AUC up 35%). Sirolimus is extensively distributed into erythrocytes with a blood to plasma ratio of 36.

Sirolimus is a substrate for both CYP3A4 and P-glycoprotein, and it undergoes extensive O-demethylation and/or hydroxylation primarily in the liver. The elimination half-life in renal transplant patients appears to be about 62 hours (longer in males than females). Administration of a loading dose three times the maintenance dose will provide near steady state concentrations within 1 day in most patients. The major route of excretion appears to be via the feces. Liver disease has been shown to result in a higher AUC (61%) and a longer half-life (43%). Dose requirement will probably be lower in the presence of hepatic disease.

Contraindications and cautions. Sirolimus must be used with caution in patients with pre-existing dyslipidemias or hepatic disease. Baseline, fasting cholesterol and triglyceride levels should be obtained before or shortly following initiation of sirolimus therapy, and should be routinely monitored thereafter. Sirolimus can cause leukopenia and thrombocytopenia, and it should not be used in patients with ongoing infections. Sirolimus is pregnancy category C, but it should be used with extreme caution in women with childbearing potential.

Dosage and administration. Sirolimus (Rapamune®) is commercially available as an oral solution formulated in an oil base and containing 1 mg/mL of sirolimus. Sirolimus should be taken 4 hours after the CSA dose, and should be taken consistently either with or without food. If sirolimus is combined with tacrolimus (instead of CSA), the two drugs may be taken at the same time. The correct amount of sirolimus solution should be added to 60 mL of water or orange juice in a glass or plastic container, stirred vigorously and taken at once. The container should be refilled with 120 mL of water, stirred vigorously, and taken at once. Only water or orange juice should be used. Grapefruit juice should be avoided since it can significantly alter sirolimus kinetics.

When used in combination with CSA, the recommended adult loading dose of sirolimus is 6 mg (3x the maintenance dose). A loading dose is recommended because of the drug's long half-life; without a loading dose it may take 2 weeks to reach steady state. The recommended adult maintenance dose is 2 mg/day. The recommended maintenance dose for children 13 years of age or older is 1 mg/m^2 of BSA per day. A loading dose (3x the maintenance dose) may also be necessary. Patients with significant hepatic impairment are expected to require lower doses. Like tacrolimus and cyclosporine, sirolimus should be dosed by serum levels. The target 18-hour trough level is between 5 and 15 ng/mL, and is generally adjusted for the type of transplant and the time elapsed since the transplant.

Main side effects. Hypercholesterolemia and hypertriglyceridemia occur in approximately 50% of patients treated with CSA and sirolimus. The incidence of this metabolic complication appears to be dose-related occurring more commonly in patients receiving high sirolimus doses (in combination with CSA). All patients receiving sirolimus should be monitored for hyperlipidemia during therapy. Hematologic adverse effects of sirolimus include thrombocytopenia, leukopenia, and to a lesser extent anemia. Hypertension is also frequent.

In the phase III clinical trials, the patients treated with the higher doses of sirolimus (5 mg/day) had a higher incidence of anemia, arthralgia, diarrhea, hypokalemia, epistaxis, insomnia, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome, skin ulcer, herpes simplex and facial edema. The combination of cyclosporine A and

sirolimus is associated with a potentiation of CSA-induced nephrotoxicity, but the mechanism remains unclear. Skin rash occurs in a significant number of patients within a few days of the initiation of sirolimus therapy. More recently, inerstitial pneumonitis has been reported [NEMJ 2000; 343(24):1815].

Pharmacodynamic drug interactions. Sirolimus may potentiate the nephrotoxic effects of CSA, and cause higher serum creatinine levels in patients who are also taking CSA. Exacerbation of hematologic toxicity may occur with acyclovir, ganciclovir carbamazepine, clozapine and co-trimoxazole therapy (leukopenia, thrombocytopenia).

Pharmacokinetic drug interactions. Adverse drug reactions associated with high sirolimus levels (thrombocytopenia, hyperlipidemia, hypertension, tremor, infections, etc.) are likely to be precipitated or exacerbated by the addition of agents that inhibit sirolimus metabolism via the CYP3A4, increasing its bioavailability and reducing its clearance. These include ketoconazole, itraconazole, erythromycin, clarithromycin, cimetidine, grapefruit juice, danazol, nefazodone (Serzone®), diltiazem, verapamil and others (see Tables 3 and 5). In contrast, an increased risk of acute allograft rejection is associated with use of agents that increase sirolimus metabolism (via CYP3A4 induction), accelerating its clearance and lowering its level. These include the anti-epileptic drugs (carbamazepine, phenytoin, phenobarbital), rifampin, rifabutin, St. John's Wort and others (see Tables 4 and 5).

Because of the higher risk of developing hyperlipidemia, transplant patients receiving sirolimus are more likely to be treated with lipid-lowering drugs. The risk of myopathy (myositis and rhabdomyolysis) may be increased when an HMG-CoA reductase inhibitor like lovastatin and simvastatin is added to the drug regimen of a transplant patient maintained on CSA. Phase III studies of sirolimus have shown that patients on sirolimus therapy can be safely treated with HMG-CoA reductase inhibitors. Although there are no published reports of increased incidence of rhabdomyolysis with sirolimus, patients should be educated about the symptoms of muscle damage and should report any muscle problems.

Tacrolimus (Prograf). Tacrolimus is a macrolide compound produced by fungus (*Streptomyces tsukubaensis*) and possesses strong immunosuppressive properties. It is FDA indicated for the prevention of organ rejection in patients receiving allogeneic liver or kidney transplants. However, its use has expanded to other organs including heart, pancreas and small bowel. It is recommended that tacrolimus be used as part of an immunosuppressive regimen that includes a steroid such as prednisone.

Tacrolimus is the first calcineurin-inhibiting immunosuppressive agent after CSA to be introduced into clinical practice. Like cyclosporine, tacrolimus achieves its effects on the immune system by inhibiting calcineurin, a phosphatase required for the production of interleukin-2 (IL-2). Suppression of IL-2 production impairs the early stages of the activation and proliferation of helper and cytotoxic T cells. In short, tacrolimus works mainly by preventing the activation and proliferation of T cells.

Tacrolimus is available in both oral and injectable forms. The oral dose is roughly four times larger than the IV dose. The use of the IV form is restricted to situations where the oral forms (capsules or extemporaneously prepared suspension) cannot be administered to the patients. The oral dose ranges from 0.1 to 0.2 mg/kg/day (usually divided bid). The absorption of tacrolimus from the gastrointestinal tract is incomplete and variable, and it is subject to significant pre-systemic metabolism. The absolute oral bioavailability is approximately 20%. There is a nearly linear relationship between the dose and peak levels or AUC of tacrolimus. Also, there is a good correlation between the whole-blood trough level and the AUC. Therefore, measuring the trough level provides a convenient means of monitoring the level of exposure of the body to the immunosuppressive effects of tacrolimus. The target trough level varies generally between 5 and 15 ng/mL, depending on multiple factors including the type of transplant and the time elapsed since the transplant. The trough is maintained closer to the higher end of the range in the early post-transplant period or when an acute rejection is detected or suspected, or when the risk of acute rejection is deemed to be high. Lower levels (5-8 ng/mL) provide sufficient protection against rejection in stable patients several months or years after the transplant or in patients on "triple therapy" regimen that includes mycophenolate or sirolimus.

Main side effects. Like cyclosporine, tacrolimus may be nephrotoxic. Hypertension, hyperkalemia,

hypomagnesemia and hyperuricemia have also been reported. Relative to cyclosporine, tacrolimus may be associated with increased incidence of neurotoxicity, including tremors and headache, and rarely confusion and seizures. GI side effects (nausea, vomiting, abdominal pain, diarrhea etc.) may occur at the higher tacrolimus blood levels. These may be more frequent in patients on tacrolimus and MMF combined therapy. Finally, alopecia, pancreatitis and hepatotoxicity have rarely been reported.

Pharmacodynamic drug interactions involving tacrolimus. Additive nephrotoxicity can occur if tacrolimus is administered with other nephrotoxic drugs such as amphotericin B, acyclovir, aminoglycosides, foscarnet, co-trimoxazole (SMX-TMP) and nonsteroidal anti-inflammatory drugs (NSAIDs). Neurotoxicity (confusion, tremor, agitation and seizures) may be increased when imipenem is administered to tacrolimus-treated patients. Meropenem may be a safer carbapenem for transplant patients receiving tacrolimus. There is an increased risk of hyperkalemia when tacrolimus is combined with potassium-sparing diuretics (e.g., spironolactone, amiloride and triamterene), ACE-inhibitors or angiotensin II receptor blockers. Hypophosphatemia and hypomagnesemia can occur when tacrolimus is used with loop diuretics, aminoglycosides, or amphotericin B and oral supplementation may be required in some patients..

Pharmacokinetic drug interactions involving tacrolimus. Adverse drug reactions associated with high tacrolimus levels (nephrotoxicity, neurotoxicity, hypertension, infections, etc.) are likely to be precipitated or exacerbated by the addition of agents that inhibit tacrolimus metabolism via the CYP3A4, increasing its bioavailability and reducing its clearance. These include ketoconazole, itraconazole, erythromycin, clarithromycin, cimetidine, grapefruit juice, danazol, nefazodone (Serzone®), diltiazem, verapamil and others (see Tables 3 and 5).

There is an increased risk of acute allograft rejection with use of agents that increase tacrolimus metabolism (via CYP3A4 induction), accelerating its clearance and lowering its level. These include the anti-epileptic drugs (carbamazepine, phenytoin, phenobarbital), rifampin, rifabutin, St. John's Wort (SJW) and others (Tables 4 and 5). Cases of acute rejection have been reported in heart transplant patients after several weeks of daily intake of the SJW extract. Transplant patients must avoid taking phytopharmaceuticals and "nutritional" supplements until they are proven safe.

The risk of myopathy (myositis and rhabdomyolysis) is increased when a lipid-lowering drug like lovastatin and simvastatin is added to the drug regimen of a transplant patient. Although this complication has been limited largely to patients maintained on CSA, it is prudent to keep a high index of suspicion when tacrolimus is the primary immunosuppressant. Liver function tests plus creatine kinase (CK-MM isozyme) and lactic dehydrogenase should be determined periodically in transplant patients receiving a statin. Patients should be educated about the symptoms of muscle damage and should report any muscle problems.

Unlike cyclosporine, tacrolimus does not appear to affect the absorption and the bioavailability of sirolimus. This suggests that when sirolimus is used in combination with tacrolimus rather than with CSA, higher doses of sirolimus may be required to achieve the same target trough level.

Summary

Drug interactions are common with immunosuppression medications and may precipitate organ rejection or toxicity. Common interactions involve agents that have pharmacokinetic and pharmacodynamic interactions or alter the absorption of immunosuppressive medications. Knowledge of such interactions is essential when prescribing non-immunosuppressive medications for the well transplant patient.

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