Drug Therapy in the Heart Transplant Recipient
Part IV: Drug–Drug Interactions

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With improving survival, the heart transplant recipient faces an increasing number of medical problems caused by both aging and the cumulative complications of immunosuppressive drugs.[1] The availability of new drugs to treat infection, obesity, hypertension, hyperlipidemia, renal insufficiency, diabetes, osteoporosis, gout, and malignancies has resulted in the heart transplant recipient and their physicians facing an almost overwhelming number of important drug–drug interactions. In parts 1 through 3 of this series, we reviewed commonly used immunosuppressive drugs and their pharmacology, as well as the common medical problems faced by the heart transplant recipient. In this article, we provide an overview of the mechanisms of common and important potential drug–drug interactions and guidelines for avoiding these interactions.

Principles of Drug–Drug Interactions

The risk for drug–drug interactions is increased by advanced age, polypharmacy, medications with a narrow therapeutic index, or medications requiring intensive monitoring. All of these factors except advanced age are present in the heart transplant recipient. A 10-fold interpatient variability may exist in the magnitude of a drug interaction resulting from patient-related and drug-related factors.[2]

Patient-related factors predisposing to drug interactions include concomitant diseases, genetics, diet, and environmental exposures. For example, commonly used immunosuppressants, antifungal agents, and lipid-lowering medications are metabolized through the cytochrome P450 (CYP450) enzyme system and effluxed from cells by the multiple drug resistance transporter protein p-glycoprotein (P-gp). Both systems are found in the liver and gastrointestinal tract and exhibit genetic polymorphism.[2] The CYP450 enzymes belong to a superfamily of oxygenases; the primary purpose of these oxygenases is to add a functional group to a drug to increase its polarity and to promote its excretion from the body. If enzymes possess >40% homology, they are grouped together into families designated by an Arabic numeral (eg, the CYP1 family). Families are further divided into subfamilies, which are designated by a letter after the number (eg, CYP2C and CYP2D subfamilies); members of each subfamily have >55% homology with each another. Individual members are given an additional number (eg, CYP3A4) to identify a specific enzyme pathway.[2] CYP3A4 is particularly important because 60% of oxidized drugs, including the calcineurin inhibitors (CIs) cyclosporine (CSA) and tacrolimus (TAC), sirolimus (SIR), and everolimus (EVER), undergo biotransformation through this particular enzyme system.[3]

P-gp is a membrane-bound glycoprotein belonging to the superfamily of ATP-binding cassette transporters. Like the CYP450 enzyme system, P-gp acts in a protective capacity by "effluxing" drug from the cell membrane or cytoplasm. P-gp density is highest within the small intestine, proximal tubules of the kidney, and biliary canalicular membranes. Some medications such as CIs and SIR use both the CYP450 enzyme system and P-gp, making them especially susceptible to drug interactions.[4] Substrates, inhibitors, and inducers of the CYP450 enzyme system and P-gp have been extensively reviewed elsewhere.[4]

Drug-related variability may be dependent on dose, duration, sequence of administration, and timing of concomitant medications.[2] Drug interactions may be pharmacokinetic or pharmacodynamic in nature. After oral administration, several intricate elements are involved with the absorption of a drug, all of which can be possible targets for drug–drug interactions: intestinal delivery (gastric pH, gastric emptying, and presence of food), intestinal luminal absorption (drug dissolution, lipophilicity, and stability), active intestinal drug-efflux pumps and metabolism (P-gp, CYP450 enzyme system), and hepatic first-pass metabolism (phase I and II metabolism)[1] (Figure). Pharmacokinetic interactions involve these alterations to the absorption, distribution, metabolism, or elimination of a drug. Pharmacokinetic parameters commonly used to evaluate drug interactions are the area under the curve (AUC), which reflects medication bioavailability, and mean maximum blood concentrations for the dosing interval (Cmax). Pharmacodynamic interactions occur when a drug potentiates or diminishes the effect of another.[5]

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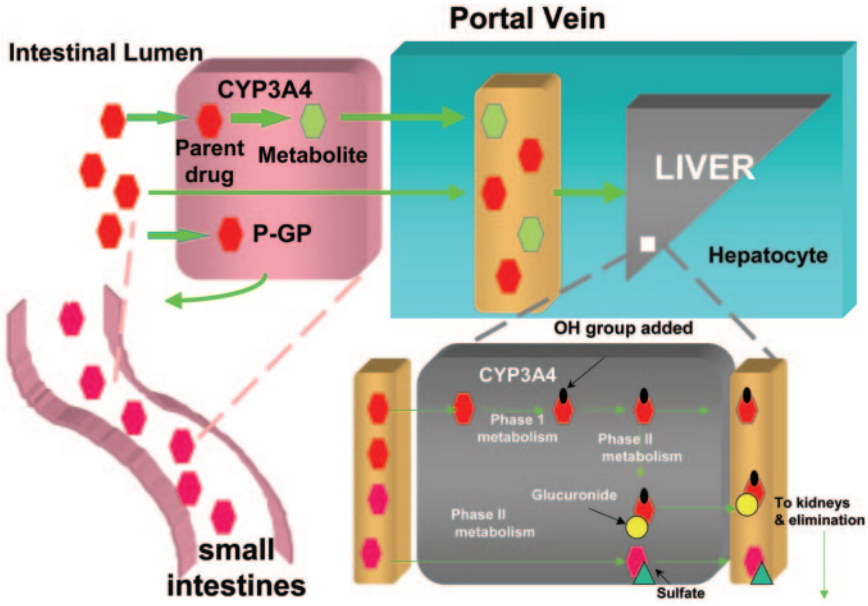

Drug metabolism and countertransport by P-gp. During absorption, drugs are metabolized by intestinal cytochrome P450. P-gp assists by pumping drug back into intestinal lumen. Drugs that evade intestinal metabolism enter portal blood and are subject to further biotransformation by hepatic cytochrome P450. Most drugs undergo phase I metabolism in which metabolites may be further conjugated or are directly eliminated by kidney. Small group of drugs may undergo phase II metabolism with no prior biotransformation. Modified with permission from Reference 2.

Using case reports, case series, package inserts, and in vivo pharmacokinetic studies in these subjects, we provide a clinically relevant list of the pharmacokinetic and dynamic drug interactions with immunosuppressant medications (Table 1). Interactions were selected on the basis of widespread use of the interacting medication in the heart transplant population and the potential for the interaction to cause an adverse event defined as death, hospitalization, rejection, therapeutic failure, and/or prolonged hospital stay. Table 2 defines criteria used to evaluate onset of action, magnitude of effect, and strength of evidence for interactions discussed.[6]

Therapeutic Drug Monitoring

Monitoring of trough levels is standard with CI. Drug level monitoring has not guided therapy in clinical trials of SIR or mycophenolate mofetil (MMF), but some guidelines have been suggested.[7,8] The recommended frequency of monitoring of immunosuppressive drug levels depends on several factors, including the potential magnitude and clinical consequences of the interaction and the timing of onset of the interaction. Patients are most susceptible to rejection in the first few months after transplantation or if they have had frequent episodes of rejection; monitoring for a decrease in immunosuppressive drug levels may need to be more frequent in these patients.[9] Overall, recommended monitoring of drug levels may vary from 1 to 3 times per week for the first week and occur less frequently in follow-up, depending on these important patient factors and the magnitude and timing of the interaction.

Calcineurin Inhibitors

CSA and TAC Interactions

Pharmacokinetic

More studies report drug interactions with CSA than with TAC, in large part because of its earlier availability for clinical use. Interactions reported for CSA are likely to be present with TAC.

Oral CSA and TAC have incomplete, erratic absorption with a large interpatient variability. Both agents are extensively metabolized by hepatic and intestinal CYP3A and act as both inhibitors and substrates for P-gp.[10,11]

Antihypertensives

Diltiazem and verapamil inhibit both CYP3A4 and P-gp, increasing CSA and TAC concentrations by 1.5- to 6-fold and thus requiring a 20% to 75% dose reduction in CSA and TAC.[10,12–19] Because many of the dihydropyridine calcium channel blockers are substrates of CYP3A4 and inhibitors of P-gp, potential interactions with CSA also exist. Amlodipine, felodipine, and nicardipine can increase CSA concentrations between 23% and 350%.[20–26] Felodipine and nifedipine have been documented to increase TAC levels by >50%.[27,28] Although nifedipine and isradipine do not appear to affect CSA pharmacokinetics, caution is still warranted when any of the dihydropyridines with TAC or CSA are initiated or discontinued.[29,30]

Lipid-Lowering Agents

Atorvastatin, simvastatin, and lovastatin are all substrates for CYP3A4, predisposing them to pharmacokinetic interactions with CSA and TAC, potentially leading to myotoxicity (ie, myopathy and/or rhabdomyolysis).[31] Fluvastatin is metabolized primarily by CYP2C9 and pravastatin through multiple pathways not completely involving the CYP enzyme system. Atorvastatin, lovastatin, and pravastatin are also substrates of P-gp.[4] Rosuvastatin, which was recently approved, exhibits minimal metabolism via the CYP enzyme system.[32]

Except for fluvastatin, all the statins have been associated with rhabdomyolysis when used in combination with CSA.[31] Although the mechanism remains unknown, the incidence of myotoxicity increases with increasing statin dose.[31,33] Limited information is available about rhabdomyolysis with TAC and statins. In solid-organ transplant recipients, CSA combined with lovastatin, simvastatin, fluvastatin, atorvastatin, or

TABLE 1. Pharmacokinetic Interactions With Commonly Used Immunosuppressants

Drug	Interaction Drug	Effect	Onset	Magnitude	Level of Evidence	Management*
CSA† TAC‡	**Antihypertensives**[10,12–28]					Monitor CSA/TAC levels 3 times a week for first week; reduce CSA/TAC accordingly. With diltiazem and verapamil, decrease CSA/TAC dose by 20%–50%.
	Diltiazem†‡	Increased TAC/CSA exposure; with TAC subsequent neurological toxicity	Delayed	II	A (CSA) C (TAC)	
	Verapamil†	Increased TAC/CSA exposure	Delayed	II	A	
	Amlodipine†	Increased TAC/CSA exposure	Delayed	II	D	
	Felodipine†‡	Increased TAC/CSA exposure	Delayed	II	D (CSA) D (TAC)	
	Nifedipine‡	Increased TAC exposure	Delayed	II	D	
	Nicardipine†	Increased TAC/CSA exposure	Delayed	II	D	
	Lipid-lowering agents[31,34–41,46,49,50]					Use lowest possible statin dose; consider fluvastatin or pravastatin.
	Atorvastatin†	Increased statin exposure, increased risk for myopathy/rhabdomyolysis	Delayed	I	C	
	Fluvastatin†	Increased statin exposure, possible increased risk for myopathy/rhabdomyolysis	Delayed	I	D	
	Lovastatin†	Increased statin exposure, increased risk for myopathy/rhabdomyolysis	Delayed	I	B	
	Pravastatin†	Increased statin exposure, possible increased risk for myopathy/rhabdomyolysis	Delayed	I	D	
	Rosuvastatin†	Increased statin exposure, increased risk for myopathy/rhabdomyolysis	?	I	D	
	Simvastatin†	Increased statin exposure, increased risk for myopathy/rhabdomyolysis	Delayed	I	B	
	Ezetimibe†	Increased ezetimibe exposure	?	III	D	Use lowest possible ezetimibe dose.
	Gemfibrozil†	Decreased CSA/TAC exposure	Delayed	II	D	Monitor CSA/TAC levels 2–3 times weekly for first week, once weekly for the first month, then periodically thereafter.
	Fenofibrate†	Decreased CSA/TAC exposure	Delayed	II	D	Monitor CSA/TAC levels 2–3 times weekly for first week, once weekly for first month, then periodically thereafter.
	Antiplatelet agents[51,52,54]					
	Ticlopidine†	Decreased CSA/TAC exposure	Delayed	II	D	Monitor CSA/TAC levels closely for several months.
	Clopidogrel†	Decrease in active metabolite of clopidogrel	?	II	D	Monitor for increased clotting.
	Antifungal agents[10,56–59]					
	Azole antifungals					
	Clotrimazole (trouches)‡	Increased CSA/TAC exposure	Delayed	II	D	Monitor CSA/TAC levels 2–3 times for first week.
	Fluconazole†‡	Increased CSA/TAC exposure	Delayed	II	D (CSA) D (TAC)	Monitor CSA/TAC levels 2–3 times for first week.
	Itraconazole†‡	Increased CSA/TAC exposure, subsequent nephrotoxicity	Rapid	II	B (CSA) B (TAC)	Monitor CSA/TAC levels 2–3 times for first week; reduce initial dose of CSA/TAC by 50%.
	Ketoconazole†‡	Increased CSA/TAC exposure with subsequent renal and hepatic toxicity, glucose intolerance, gingival hyperplasia with CSA	Rapid	II	B (CSA) B (TAC)	Monitor CSA/TAC levels 2–3 times for first week; reduce initial dose of CSA/TAC by 50%.
	Voriconazole†‡	Increased CSA/TAC exposure	Rapid	II	C (CSA) C (TAC)	Monitor TAC/CSA levels 2–3 times for first week; reduce initial dose of CSA by 50% and TAC by 33%.
	Other antifungal agents					
	Caspofungin†‡	Increased caspofungin exposure, with subsequent hepatoxicity	Rapid	II	D (CSA) D (TAC)	Avoid with CSA; with TAC, monitor TAC levels and liver function tests closely.
	Antidepressants[60–65,67]					
	Nefazodone†‡	Increased CSA/TAC exposure with subsequent renal and hepatic toxicity; with TAC also neurological toxicity	Delayed	II	B (CSA) C (TAC)	Avoid combination; consider alternative agent such as sertraline, mirtazapine, paroxetine, citalopram, or venlafaxine.
	Fluvoxamine†	Increased CSA/TAC exposure	Delayed	II	C	Monitor CSA/TAC 2–3 times a week for the first 2 weeks.
	Fluoxetine†	Increased CSA/TAC exposure	Delayed	II	C	Monitor CSA/TAC 2–3 times a week for the first 2 weeks.
	St. John's Wort†‡	Decreased CSA/TAC exposure with subsequent rejection with CSA	Delayed	I	C (CSA) C (TAC)	Avoid combination.
	Other agents[68–75,77–79]					
	Antiarrhythmics					
	Amiodarone†	Increased CSA/TAC exposure	Delayed	II	D	Monitor CSA/TAC levels every 3 d for first week, weekly for first month, then periodically thereafter; use lowest possible dose of CSA, TAC, and amiodarone.

continues

TABLE 1. Continued

Drug	Interaction Drug	Effect	Onset	Magnitude	Level of Evidence	Management*
	Anticonvulsants					Monitor TAC/CSA levels 2–3 times a week for first 2 wk; consider alternative agent such as valproic acid, gabapentin, lamotrigine, tiagabine, vigabatrin. Monitor bound and free phenytoin levels closely, especially in combination with TAC; increase CSA dose 2-fold before beginning phenytoin.
	Carbamazepine†‡	Decreased TAC/CSA exposure	Delayed	II	D (CSA) D (TAC)	
	Oxcarbazepine†	Decreased TAC/CSA exposure	Delayed	II	D	
	Phenytoin†‡	Decreased TAC/CSA exposure, increased phenytoin concentrations	Delayed	II	C (CSA) D (TAC)	
SIR§ EVER‖	**Antihypertensives[86,87]**					
	Diltiazem§	Increased SIR exposure	Delayed	II	C	Monitor SIR levels 3 times a week for first week.
	Antifungal agents [87–89]					
	Fluconazole§	Increased SIR/EVER exposure	Delayed	II	D	Monitor SIR levels for 1–2 weeks.
	Itraconazole§, ‖	Increased SIR/EVER exposure	Delayed	II	C (SIR) C (EVER)	Monitor SIR levels for 1–2 weeks.
	Ketoconazole§	Increased SIR/EVER exposure	Delayed	II	C	Avoid combination.
	Voriconazole§	Increased SIR/EVER exposure	Delayed	II	C	Avoid combination.
	Other agents[90–92]					
	CSA§‖	Increased SIR/EVER exposure	Rapid	II	B (SIR) C (EVER)	Administer SIR 4 h after CSA.
MMF	**Lipid-lowering agents[98]**					
	Cholestyramine	Decreased MPA exposure	Rapid	II	D	Avoid concomitant use.
	Other agents[99,100,101–106]					
	CSA	Decreased MPA exposure	Delayed	II	C	Monitor MPA levels (controversial).
	TAC	Decreased MPA exposure	Delayed	II	C	Monitor MPA levels (controversial) and s/s of MMF toxicity.
	Iron/antacids	Decreased MPA exposure	Rapid	II	C	Stagger MMF and iron/antacid preparations by 2–4 h.
Azathioprine	**Antigout agents[108]**					
	Allopurinol	Increased exposure to 6-MP with subsequent anemia, leukopenia, thrombocytopenia	Delayed	I	A	Decrease AZA dose by 75%–80%.
	Other agents[109–111]					
	Warfarin	Decreased INR/PT	Delayed	II	D	INR/PT should be monitored at least 2 times weekly for first week.

AZA indicates azathioprine; PT, protime; INR, international normalized ratio; and s/s, signs and symptoms.

*The frequency in obtaining immunosuppressant concentrations may vary, depending on patient's clinical stability, time from transplantation, or rejection history.
†Reported with CSA; ‡reported with TAC; §reported with SIR; ‖reported with EVER.

rosuvastatin increased statin AUC by 3- to 20-fold compared with baseline.[34–41] Compared with other HMG CoA reductase inhibitors, pravastatin combined with CSA appears to have minimal accumulation after multiple dosages.[42,43] In the liver and small intestine, the affinity of TAC for CYP3A is comparable to that of lovastatin and simvastatin; therefore, a potential interaction exists.[44]

When used in combination with CSA, the lowest dose possible of lipid-lowering agent should be prescribed consistent with package labeling and clinical trials.[31,45] Although no formal dosing recommendations have been made with TAC, the same recommendation seems prudent. Fluvastatin or pravastatin may be the safest of the statins in transplant recipients. Should rhabdomyolysis occur, the statin, CSA, TAC, and other myotoxic agents should be discontinued immediately.[31]

In a single report, CSA increased ezetimibe concentrations 12-fold. Further evaluation of interactions of ezetimibe with the CI is necessary before recommendations can be made.[46]

The fibric acid derivatives gemfibrozil and fenofibrate are metabolized by CYP3A4 and excreted renally.[47] Data demonstrating potential drug interaction between gemfibrozil or fenofibrate and CSA are conflicting.[48] Studies suggest an 18% to 27% reduction in CSA trough levels with concomitant fibric acid use.[49,50] Although reports of myotoxicity with CSA are few, the potential exists. The combination of statin and a fibrate may result in myotoxicity; the risk is even greater when a CI is added.[31]

Antiplatelet Agents

Ticlopidine (250 to 500 mg) may reduce CSA concentrations by 1.4- to 2.0-fold over days to months as a result of possible ticlopidine induction of CYP3A.[51,52] Not all studies have confirmed this interaction.[53] Currently, no data with TAC have been published. Nonetheless, CSA and TAC concentrations should be monitored closely for several months when ticlopidine is initiated or discontinued. Coadministration with CSA or TAC may decrease the active

TABLE 2. Definitions of Onset of Action, Magnitude of Effect, and Relative Strength of Evidence for Immunosuppressant Drug Interactions[6]

Onset of action	
Rapid	PCK effect is demonstrated within 24 h of coadministration.
Delayed	PCK effect will not be demonstrated until interacting drug is administered for days or weeks.
Magnitude of effect	
Major (I)	Effects that are life threatening or capable of permanent damage, rejection
Moderate (II)	May cause a detriment in clinical status, additional treatment, hospitalization, or extension of stay
Minor (III)	Effects may be mild, consequences may be bothersome or noticeable; additional treatment not required; no sign of effect on therapeutic outcomes
Relative strength of evidence	
Established (A)	Proven to occur in well-controlled studies. Altered pharmacological effect has been demonstrated in well-controlled trials.
	or
	PCK effect has been demonstrated in well-controlled human studies. Altered pharmacological response is expected from magnitude of kinetic effect or because clinical observations support occurrence of the interaction.
Probable (B)	Very likely, but not proven clinically. A PCK interaction has been demonstrated in well-controlled studies (Based on magnitude of kinetic changes and known plasma level–response relationship of the affected drug, an altered pharmacological response will probably occur).
	or
	When controlled human experimentation is impractical, well-designed animal experiments confirm an interaction that is suggested by multiple case reports or uncontrolled studies
Suspected (C)	May occur, some good data but needs further study. A PCK interaction has been demonstrated in well-controlled studies. Although an altered pharmacological response might be expected from magnitude of kinetic change, no firm conclusion can be drawn because a plasma level–response relationship has not been established for the affected drug.
	or
	An altered pharmacological response has been reported in multiple case reports or repeated uncontrolled clinical studies.
Possible (D)	Could occur, but data are very limited. Although a PCK interaction has been demonstrated, the kinetic changes are of such magnitude that it is not possible to predict whether an altered response will occur; the evidence is divided as to whether an interaction exists.
	or
	An altered pharmacological response is suggested by limited data.

PCK indicates pharmacokinetic.

metabolite of clopidogrel, leading to a theoretical reduction in antiplatelet effect.[54]

Antifungal Agents

Ketoconazole, itraconazole, fluconazole, and voriconazole all inhibit CYP3A. Both ketoconazole and itraconazole also inhibit P-gp. In vitro, ketoconazole is the most potent inhibitor of CSA metabolism, followed by itraconazole and fluconazole.[55] Ketoconazole, itraconazole, voriconazole, and fluconizole (in doses >200 mg) can increase CSA and TAC trough concentrations by ≥2-fold.[10,56,57] With ketoconazole and itraconazole, CSA and TAC dose should be reduced initially by 50%. Specifically with voriconazole, CSA dose should be reduced by 50% and TAC dose by ≥33%.[58]

CSA may increase the caspofungin AUC by 35%, resulting in transient but clinically significant increases in liver transaminases. Currently, package labeling recommends that caspofungin not be given with CSA; however, a single-center study found that the concurrent use of caspofungin and CSA had no attributable adverse effects.[58,59] In a phase 1 study, caspofungin reduced TAC AUC by 20%, Cmax by 16%, and 12-hour blood concentration by 26%, with a small transient increase in alanine transaminase.[58] TAC should be closely monitored when caspofungin is coadministered, and TAC dose should be adjusted accordingly.[58,59]

Antidepressants

Nefazodone, fluvoxamine, and fluoxetine are potent inhibitors of CYP3A4 and may increase CSA concentrations between 2- and 10-fold.[60–62] Only nefazodone has been reported to increase TAC concentrations ≥2- to 5-fold; however, a similar effect would be expected with fluvoxamine and fluoxetine.[63,64] Sertraline, mirtazapine, and paroxetine are weak inhibitors of CYP3A4; citalopram, a substrate for CYP3A4, and venlafaxine, a substrate and inhibitor of CYP2D6, may be potential alternatives.[65] With numerous antidepressants available, nefazodone should be avoided in patients receiving CSA and TAC. Because of the lack of data, fluoxetine and fluvoxamine should be used with caution when combined with CSA or TAC.

In animal and in vitro studies, St. John's Wort may increase the expression of intestinal P-gp by 3.8-fold and may have a similar effect on CYP3A4.[66] Case reports have documented a 2- to 6-fold reduction in CSA and TAC concentrations in transplant recipients, leading to possible organ rejection.[67] On the basis of these data and the questionable efficacy of St. John's Wort, this

agent should be avoided.

Other Agents

Amiodarone, CSA, and TAC are all substrates for and inhibitors of P-gp. Amiodarone, CSA, and TAC are also substrates for CYP3A4; however, only amiodarone is considered a CYP3A4 inhibitor.[4] Therefore, the possibility for simultaneous accumulation and increased toxicity for CI and amiodarone exists. In a heart transplant recipient, a 50% reduction in CSA clearance with a subsequent 1.8-fold increase in trough concentrations was demonstrated with concomitant amiodarone.[68] Another report found a doubling of CSA concentrations within 3 days of initiation of amiodarone.[69] This effect of amiodarone on CSA pharmacokinetics may last >4 weeks after amiodarone therapy is discontinued.[70] No data exist for amiodarone and TAC, but a similar interaction likely is present. When amiodarone is added to a CI, the lowest possible dose of amiodarone should be used, and CI levels should be monitored carefully for ≥4 weeks.

Oral phenytoin may significantly reduce CSA Cmax, mean elimination half-life, and AUC.[71] Although not fully studied, the same effect would be expected with TAC.[72] This interaction may be due to CYP3A induction and/or possible interference with CSA absorption. It has been suggested that substitution of intravenous for oral CSA might prevent this interaction.[73] However, in a pediatric bone marrow transplant recipient, changing from an oral to an intravenous formation did not improve CSA concentrations.[74] Elevated phenytoin concentrations have been reported with concomitant use of phenytoin and TAC, possibly because of phenytoin protein displacement by TAC.[72,75] Because both TAC and CSA are highly protein bound, the same effect should occur with CSA. When phenytoin is initiated or discontinued, TAC or CSA concentrations should be monitored closely for the first 2 weeks. A 2-fold increase in CSA dose should be made before initiation of phenytoin.[76]

Carbamazepine, a potent inducer of the CYP enzyme system, may reduce CSA levels by ≥4-fold. CSA levels may not return to baseline for up to 4 months after carbamazepine is discontinued.[77] The same effect should be expected with oxcarbazepine.[78] Although not reported, reductions in TAC concentrations should also be anticipated.[79] Alternative antiepileptics that do not inhibit the CYP3A system are valproic acid, gabapentin, lamotrigine, tiagabine, and vigabatrin.[78]

Pharmacodynamic

Antigout Agents

A combination of side effects consisting of gastrointestinal dysfunction, hepatonephropathy, and neuromyopathy may be induced by combining colchicine with CSA. This syndrome appears within 1 to 2 weeks of initiation of colchicine (0.6 to 3.6 mg/d) and resolves within 3 to 4 weeks of discontinuing colchicine and/or reducing the CSA dose. Patients with renal dysfunction appear to be particularly susceptible.[80] It has been postulated that CSA may potentate the toxic effects of colchicine by inhibiting P-gp thereby reducing the renal, hepatic, and biliary clearance and efflux of colchicine and its metabolites from cardiac and skeletal muscle. Therefore, colchicine should be used briefly and in the lowest possible dose with CI. Patients should be carefully monitored for signs of nausea, vomiting, jaundice, muscle weakness, muscle wasting, myalgias, and distal paresthesias.[80] If any of these symptoms arise, colchicine should be immediately discontinued.

Other Agents

Additive nephrotoxicity has been noted when trimethoprim sulfamethoxazole, trimethoprim, amphotericin B, aminoglycosides, foscarnet, nonsteroidal anti-inflammatory agents, or ACE inhibitors were added to CSA or TAC.[81–83]

Target of Rapamycin Inhibitors

SIR/EVER Interactions

Pharmacokinetic

SIR and EVER are macrolide immunosuppressants. EVER was recently approved for use in heart transplant recipients. Although it is related to SIR, it is structurally different.[84] Both SIR and EVER are rapidly absorbed after oral administration; however, SIR exhibits a low oral bioavailability (14%) because of its extensive intestinal and hepatic metabolism by CYP3A4 and countertransport by intestinal P-gp.[85] Few drug interactions with SIR or EVER have been published because of their recent introduction into clinical use. However, interactions similar to those of CSA and TAC or of greater magnitude are likely with SIR and EVER.

Antihypertensives

In a pharmacokinetic study of healthy subjects, oral diltiazem (120-mg single dose) increased mean SIR Cmax and AUC by 43% and 60%, respectively. This increase in SIR bioavailability may be due to inhibition of CYP3A4 and P-gp by diltiazem.[4,86] Observations from multicenter efficacy trials found no effect of potential CYP3A4 inhibitors such as the dihydropyridines, diltiazem, or verapamil on EVER concentrations.[87]

Antifungal Agents

The commonly used azole antifungal agents should be used carefully in combination with SIR or EVER. In healthy volunteers, ketoconazole increased SIR AUC and Cmax by 11- and 4.4-fold, respectively.[88] In a cadaveric renal transplant patient, oral fluconazole increased SIR trough concentrations 3.5-fold.[89] Package labeling recommends not administering SIR with ketoconazole or voriconazole.[90] Itraconazole may decrease EVER clearance by 71%.[87]

Other Agents

The administration time of CSA with SIR may affect SIR pharmacokinetics. In a study of stable renal transplant patients receiving SIR, CSA, and prednisolone for >3 months, the AUC, Cmax, and trough concentrations of SIR were higher when the drugs were given concomitantly compared with administration of SIR 4 hours later (459±207 versus 317±149 ng · mL^{-1} · h^{-1}, $P=0.001$; 43.8±20.6 versus 25.5±14.2 ng/mL, $P=0.002$; 13.1±7.1 versus 8.9±4.4 ng/mL, $P<0.001$, respectively). This effect was attributed to inhibition of first-pass metabolism, CYP3A4, and/or P-gp or improvement in SIR gut dispersion by CSA.[91] Package labeling recommends that SIR be administered 4 hours after CSA.[90] Coadministration of the modified CSA formulation

significantly increased EVER Cmax by 82% ($P=0.0001$) and average AUC by 168% ($P=0001$). With the oil-based CSA formulation, minor effects on EVER AUC (6%, $P=0.59$) and moderate effects on Cmax (74%, $P=0.0001$) were seen.[92] Although the precise mechanism remains unknown, close therapeutic monitoring of EVER concentrations within the first 1 to 2 weeks of the addition or removal of either formulation of CSA is required.

Pharmacodynamic

SIR and EVER may cause dose-dependent hyperlipidemia and hypertriglyceridemia, especially if combined with CSA and/or corticosteroids.[93,94] Management may include dietary restrictions, corticosteroid or SIR dose reduction, or treatment with an HMG CoA reductase inhibitor.[95] Because of its lack of CYP3A inhibition, pravastatin may be a safer option. Because the combination of a target of rapamycin inhibitor and a CI may increase the risk of nephrotoxicity, lower doses of the CI may be warranted.[96]

Antiproliferative Agents

MMF Interactions

Pharmacokinetic

MMF is rapidly absorbed after oral administration and undergoes complete metabolism to its active metabolite mycophenolic acid (MPA) by hepatic esterases. MPA is subsequently metabolized by primarily glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is devoid of pharmacological activity. Both MPAG and MMF are excreted by glomerular filtration and active tubular secretion. MPAG is also excreted into bile and may be deconjugated back to MPA by colonic bacteria, resulting in a secondary MPA peak 6 to 8 hours after the dose.[97]

Lipid-Lowering Agents

Cholestyramine may decrease MPA AUC by 40%. This decrease is probably due to binding of recirculating MPAG by cholestyramine, preventing enterohepatic circulation of MPA and loss of the secondary MPA peak. Package labeling recommends that MMF and cholestyramine not be coadministered.[98]

Other Agents

The absorption of MMF may be impaired by antacids or iron preparations because of possible chelation complex formation. When MMF is administered with antacids or iron preparations, MPA AUC and Cmax are reduced by 16.8% to 89.7% and 37.7% to 93.5%, respectively.[99,100] Therefore, doses of MMF and iron and/or antacid preparations should be staggered by 2 to 4 hours.

Although controversial, studies in renal transplant recipients receiving MMF and TAC exhibit a 1.8- to 2.3-fold increase in MPA trough concentrations and a 1.6-fold increase in MPA AUC.[101–104] Studies with CSA and MMF are variable, suggesting possible 2-fold increases or decreases in MPA trough concentrations.[105,106]

Azathioprine Interactions

Pharmacokinetic

Azathioprine, a thiopurine analog, is rapidly converted nonenzymatically into 6-mercaptopurine (6-MP), which in turn is converted into the active moiety 6-thioguanine nucleotide by the hypoxanthine phosphoribosyl–transferase pathway. Xanthine oxidase and thiopurine methyltransferase metabolize 6-MP into the inactive metabolites 6-thiouric acid and 6-methylmercaptopurine, respectively. The myelosuppression associated with azathioprine appears to be directly related to increased red blood cell levels of 6-thioguanine.[107]

Antigout Agents

Allopurinol and its active metabolite oxypurinol both inhibit intestinal and hepatic xanthine oxidase, leading to increased bioavailability and accumulation of 6-MP.[108] Several case reports have documented reversible anemia, leukopenia, and thrombocytopenia when oral azathioprine and allopurinol were given simultaneously.[108] No interaction with intravenous azathioprine has been reported. The oral dosage of azathioprine and allopurinol should be reduced by 75% to 80% when given together, and complete blood count should be closely monitored.[108]

Other Agents

In doses ≥100 mg, azathioprine may induce a resistance to warfarin anticoagulation. Cases have reported a 1.5- to 2.5-fold increase in initial weekly warfarin requirements to maintain adequate anticoagulation. Animal studies suggest an increase in prothrombin synthesis or activation by 6-MP. The concomitant use of these drugs should be accompanied by close monitoring of the protime.[109–111]

Pharmacodynamic

Antihypertensives

Anemia, leukopenia, neutropenia, and agranulocytosis may occur when ACE inhibitors are combined with immunosuppressive drugs.[112,113] Although the mechanism of this effect is unknown, hemoglobin, hematocrit, platelets, and white cell counts should be monitored every 2 to 3 weeks.

Predicting drug–drug interactions in a transplant recipient is often difficult. These patients are taking a large number of immunosuppressive and nonimmunosuppressive drugs with substantial potential for clinically significant adverse events as a result of drug–drug interactions. The guidelines provided here should help to predict and prevent these adverse events.

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