Appendix 1

Table 3 Clinically relevant pharmacokinetic drug interactions with cyclosporine (CyA)

Drug	*Data type*	*Proposed mechanism of interaction by drug*	*Clinical effect (potential or actual)*	*Recommended action*
Azole antifungals				
Fluconazole[34–42]	Case reports; PK studies	CYP3A4 inhibition	↑ CyA C_{min} → ↑ toxicity	Monitor levels. ↓ CyA dose
Itraconazole[11,43,44]			See Table 4	Monitor levels. ↓ CyA dose
Voriconazole[45]			See Table 5	Monitor levels. ↓ CyA dose
Calcium channel blockers[a] (diltiazem, verapamil)[46]	PK studies; case reports	CYP3A4 inhibition	↑ CyA C_{min} → ↑ toxicity ↓ CyA CL 50–70%	Monitor levels. ↓ CyA dose
Carbamazepine[47]	Case report	CYP3A4 induction	↓ CyA [ ] → GVHD	Monitor CyA levels. ↑ CyA dose Change to nonenzyme-inducing antiepileptic
Chloramphenicol [48]	Case report	Unknown	↑ CyA C_{min} → ↑ toxicity	Monitor CyA levels. ↓ CyA dose
Etoposide[49]		↓ Clearance of etoposide via P-glycoprotein mechanism	↑ Etoposide AUC 59% ↓ Etoposide CL 35% ↑ Etoposide $t1/2$ → > toxicity	CYA has been used to overcome P-glycoprotein resistance. No action to be taken, interaction intentional
Fluoroquinolones (norfloxacin)[b 50]	Case report	CYP3A4 inhibition	↑ CyA C_{min} → ↑ toxicity	Monitor CyA levels. ↓ CyA dose (~43%)
Imatinib mesylate	Hypothesis	CYP3A4 inhibition	Unknown, anticipate ↑ [ ] CyA	Monitor CyA levels
Macrolide antibiotics				
Clarithromycin[53,54]	Case reports	CYP3A4 inhibition	↑ CyA C_{min} 26–33%	Monitor CyA levels. ↓ CyA dose
Erythromycin[55]	Case reports	CYP3A4 inhibition	↑ CyA C_{min} 4.7-fold → toxicity	Monitor CyA levels. ↓ CyA dose by 50%
Mycophenolate mofetil (MMF)[56]	PK studies	Attenuates enterohepatic recirculation of MPAG/MPA	↓ AUC of MPA ↑ MMF C_{min} two-fold when CyA discontinued	Monitor patient for side effects of MMF
Phenytoin[57–59]	PK studies; case reports	CYP3A4 induction	↓ CyA C_{min} ↓ CyA AUC 50% → ↑ GVHD	Monitor CyA levels. ↑ CyA dose
Quinupristin/dalfopristin (QND)[60]	Case report	Unknown[c]	↑ CyA C_{min} three-fold → ↑ toxicity	Monitor CyA levels. ↓ CyA dose
Rifampin[61–63]	Healthy volunteers	CYP3A4 induction	↓ CyA AUC_{IV} 28% ↓ CyA AUC_{PO} 73% ↓ F CyA 63%	Avoid if possible ↑ CyA doses according to levels
Sirolimus[64] (oral liquid)	Healthy volunteers	CYP3A4 inhibition of sirolimus; inhibition P-glycoprotein transport	↑ Sirolimus C_{max} 116%[d] ↑ Sirolimus AUC 230%[d] ↑ Sirolimus C_{max} 37%[e] ↑ Sirolimus AUC 80%[e] → Toxicity	Administer sirolimus 4 h after administration of CyA Monitor CyA levels if necessary
Sirolimus[64] (tablets)	Healthy volunteers	CYP3A4 inhibition of Sirolimus	↑ Sirolimus C_{max} 512%[d] ↑ Sirolimus AUC 148%[d] ↑ Sirolimus C_{max} 33%[e] ↑ Sirolimus AUC 33%[e] → ↑ Toxicity	Administer sirolimus 4 h after administration of CyA Monitor CyA levels if necessary

Table 3 (Continued)

Drug	*Data type*	*Proposed mechanism of interaction by drug*	*Clinical effect (potential or actual)*	*Recommended action*
Sildenafil[65]	PK study	CYP3A4 inhibition	↑ Sildenafil C_{max} 44% ↑ Sildenafil AUC 90% ↑ $t1/2$ (elimination) → profound hypotension	Start sildenafil at 25 mg May need to adjust antihypertensives if coprescribed
St John's wort[66–72]	Case reports	CYP3A4 induction	↓ CyA C_{min} → GVHD	Avoid

[ ] = concentration; ↑ = increased; → = leads to; ↓ = decreased; AUC = area under the curve; C_{min} = trough concentration; CL = clearance; F = bioavailability; GVHD = graft-versus-host disease; PK = pharmacokinetic; CYP3A4 = cytochrome *P*450 3A4 isoenzyme.

[a] Nifedipine does not increase CyA levels and can be used safely.

[b] Ciprofloxacin [52] and levofloxacin [53] have been studied and no clinically significant interaction exists.

[c] PK of QND not known, thought to be due to CYP3A4 inhibition.

[d] Pharmacokinetic changes to sirolimus when administered *simultaneously with* cyclosporine dose.

[e] Pharmacokinetic changes to sirolimus when administered *4 h after* cyclosporine dose. MPA = mycophenolic acid.

Leather HL. *Bone Marrow Transplant*. 2004;33:137-152.

Table 2 Clinically relevant pharmacokinetic drug interactions with tacrolimus

Drug	*Data type*	*Proposed mechanism of interaction by drug*	*Clinical effect (potential or actual)*	*Recommended action*
Azole antifungals				
Fluconazole[9,10]	Case reports; PK studies	CYP3A4 inhibition	↑ Tacrolimus C_{min} → ↑ toxicity[a]	Monitor levels. ↓ Tacrolimus dose[a]
Itraconazole[11–16]			See Table 4	Monitor levels. ↓ Tacrolimus dose
Voriconazole[17]			See Table 5	Monitor levels. ↓ Tacrolimus dose
Calcium channel blockers	*In vitro*	CYP3A4 inhibition	↑ Tacrolimus AUC 26–177%	Monitor levels. ↓ Tacrolimus dose.
Diltiazem[18,19]	Case report		↑ C_{min} [ ] tacrolimus → ↑ toxicity	
Verapamil	*In vitro*	CYP3A4 inhibition	↑ Exposure → toxicity	Monitor levels. ↓ Tacrolimus dose
Chloramphenicol[20]	Case report	CYP3A4 inhibition	↑ Tacrolimus AUC 7.5-fold → toxicity	Monitor levels. ↓ Tacrolimus dose
Imatinib mesylate[21]	Abstract	CYP3A4 inhibition	Unknown, anticipate ↑ [ ] tacrolimus	Monitor levels.
Macrolide antibiotics				
Clarithromycin[22,23]	Case reports	CYP3A4 inhibition	↑ Tacrolimus C_{min} two-fold → ↑toxicity	Monitor levels. ↓ Tacrolimus dose
Erythromycin[24–26]	*In vitro*; case reports		↑ Tacrolimus C_{min} six-fold → ↑ toxicity	Monitor levels. ↓ Tacrolimus dose
Phenobarbital[27]	*In vitro*; case reports	CYP3A4 induction	↓ Tacrolimus [ ] → GVHD	Monitor levels. ↑ Tacrolimus dose
Phenytoin[28]	Case report	CYP3A4 induction	↓ Tacrolimus [ ] → GVHD	Monitor levels. ↑ Tacrolimus dose
Rifampin[29–31]	Healthy volunteers	CYP3A4 induction	↓ Tacrolimus AUC_{po} 68%	Monitor levels. ↑ Tacrolimus dose
			↓ Tacrolimus AUC_{iv} 35%	
			↓ F_{PO} 51%	
St John's wort[32]	Case report	CYP3A4 induction, ? ↑ P-glycoprotein transporter expression	↓ Tacrolimus [ ] → GVHD	Monitor levels. ↑ Tacrolimus dose
Theophylline[33]	Case report	CYP3A4 inhibition	↑ Exposure → toxicity	Monitor levels. ↓ Tacrolimus dose

[ ] = Concentration; ↑ = increased; → = leads to; ↓ = decreased; AUC = area under the curve; C_{min} = trough concentration; *F* = bioavailability; GVHD = graft-versus-host disease; PK = pharmacokinetic; CYP3A4 = cytochrome *P*450 3A4 isoenzyme.
[a]Drug interaction occurs when both agents administered orally and where fluconazole dose is >200 mg/day.

Table 2. Tacrolimus (T) and Cyclosporine (C) Pharmacokinetic Drug–Drug Interactions

Drug	Mechanism	Data Type	Effect	Recommendation
CYP inhibitors				
Amiodarone	CYP3A4 inhibition	CR; no clinical effect	Increased T/C levels at 3 days to 4 weeks	If used concurrently, monitor T/C levels and adjust dosage; need to monitor levels ≥4 weeks after adding amiodarone [53].
Azoles	CYP3A4 and P-gp inhibition	PK, CR, HSCT; renal	Increased T/C levels	Adjust dosage according to Table 5.
Estrogens	CYP3A4 inhibition	CR; no clinical effect	Increased T/C levels	If used concurrently, monitor T/C levels and adjust dosage [57].
Macrolides (not azithromycin)	CYP3A4 inhibition	CR; acute renal failure	Increased T/C levels	Avoid concurrent use; if used concurrently, monitor T/C levels [59].
Metronidazole	CYP3A4 inhibition	CR; no clinical effect	Increased T/C levels	If used concurrently, monitor T/C levels and adjust dosage [36].
Non-dihydropyridine CCBs	CYP3A4 inhibition	PK, CR; neurotoxicity	Increased T/C levels	Consider a 20% T/C dosage reduction on starting CCB; monitor T/C levels [56].
Proton pump inhibitors	CYP3A4/5 and CYP2C19 inhibition	PK, renal/liver; CR, no clinical effect	Increased T exposure	If used concurrently, monitor T level and adjust dosage [38].
Imatinib/TKIs	CYP3A4 inhibition (nilotinib–P-gp inhibition)	Animal studies	Increased T/C levels	Monitor T/C levels [43].
Aprepitant	CYP3A4 inhibition	HSCT; no clinical effect	Increased T/C levels	Monitor T/C levels [45].
Statins	CYP3A4 inhibition; OAT1B1 metabolism	Randomized, renal, healthy, CR; rhabdomyolysis with C	Increased statin AUC three- to 20-fold (depending on statin used); less interaction with T [47]	If used concurrently, consider lower initial and maintenance dose of statins; monitor for rhabdomyolysis especially with C use (stop statin immediately if it occurs) [53].
CYP inducers				
Phenytoin	CYP3A4 induction	CR; no clinical effect	Decreased T/C levels	If used concurrently, monitor T/C level and adjust dosage [58].
Competition at CYP3A				
Corticosteroids	CYP3A4/P-gp induction	CR/PK studies	Decreased T/C levels	If used concurrently, monitor T/C level during and after steroid use [46].
	CYP3A4 substrate	CR; possibly increased neurotoxicity	Increased T/C steroid levels	If used concurrently, monitor T/C level; monitor for steroid toxicity [61].
Dihydropyridine CCBs	CYP3A4 substrate; P-gp inhibitor	PK, CR; no clinical effect	Increased T/C levels (nifedipine only T)	If used concurrently, monitor T/C level [66].
Tacrolimus and cyclosporine	Competition at CYP3A4	Based on metabolism and additive toxicity	Decreased C metabolism [48]	Discontinue T/C 24 hours before initiation of the other [42].
Sirolimus	CYP3A4 competition	PK; renal, volunteers	Decreased T/C levels; increased sirolimus AUC with C	If used concurrently, monitor T level and adjust dosage; sirolimus should be administered 4 hours after oral C [51,60].
Nafcillin	CYP3A4 competition	CR; acute renal failure	Decreased C level	Avoid concurrent use (possible interference with assay) [63].
Other interactions				
MMF	Inhibition of enterohepatic recirculation	PK; liver/renal	Decreased MMF level	Use caution if administering together; MMF dosage may need adjustment [49,62].
Caspofungin	Unknown	PK; healthy, transplantation, increased liver function test values w/C	Increased T level; Increased AUC of caspofungin with C	T is favored over C for coadministration with caspofungin; routine monitoring of T level is suggested [52,64].
Octreotide	Decreased C absorption	CR; no clinical effect	Decreased C effectiveness	If used together, monitor C level; a C dosage increase of 50% at the start of octreotide is suggested [67].

PK indicates pharmacokinetic studies; CR, case reports; CCBs, calcium channel blockers.

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Appendix 2

Table 3. Sirolimus Drug–Drug Interactions

Drug	Mechanism	Data Type	Effect	Recommendation
Inhibitors				
Amiodarone	CYP3A4 inhibition	CR; no clinical effect	Increased sirolimus level	If used concurrently, monitor sirolimus level and adjust dosage [76].
Azoles	CYP3A4 and P-gp inhibition	PK, CR, HSCT; volunteers	Increased sirolimus level	Adjust according to Table 5.
Corticosteroids	CYP3A4 inhibition	PK	Increased levels of both drugs	If used concurrently, monitor sirolimus level; monitor for signs of steroid side effects [71].
Cyclosporine	CYP3A4 inhibition	PK; renal, volunteers	Increased sirolimus AUC	Sirolimus should be administered 4 hours after oral cyclosporine [60].
Macrolide antibiotics	CYP3A4 inhibition (potent)	CR; acute renal failure	Increased sirolimus level	Coadministration is not recommended [72,75].
Micafungin	Unknown	PK; volunteers	Increased sirolimus level	If used concurrently, monitor sirolimus levels and adjust dose [122].
Non-dihydropyridine diltiazem/verapamil	CYP3A4 inhibition	PK; volunteers	Increased sirolimus level	If used concurrently, monitor sirolimus level and adjust dosage [73].
Inducers				
Phenytoin	CYP3A4 induction	CR; no clinical effect	Decreased sirolimus level	If used concurrently, monitor sirolimus level and adjust dosage [74].
Competition at CYP3A				
Tacrolimus	CYP3A4 competition	Prospective/CR renal; no clinical effect	Decreased tacrolimus level	If used concurrently, monitor tacrolimus level and adjust dosage [51].

PK indicates pharmacokinetic studies; CR, case reports.

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Appendix 3

Table 5. Pharmacokinetic Effect of Azole Antifungals: Changes in AUC of Tacrolimus, Cyclosporine, and Sirolimus

	Tacrolimus		Cyclosporine		Sirolimus	
Azole	AUC	Reduction in Tacrolimus Dose	AUC	Reduction in Cyclosporine Dose	AUC	Reduction in Sirolimus Dose
Fluconazole oral 400 mg daily [30,31,33]	310% increase	50%	85% increase	40%	[a]3.5-fold increased in $C_{sirolimus}$ with 100-mg fluconazole	33%
Fluconazole i.v. 400 mg daily [5,35]	16% increase [35]	40%	21% increase [35]	25%	-	25%
Voriconazole oral or i.v. 200 mg twice daily [32,34,94]	300% increase	66%	70% increase	50%	1,000% increase	90%
Posaconazole oral 200 three times/day [68,77]	350% increase	75%	33% increase	25%	8.9-fold increase	50%

[a]Monitoring of blood levels of calcineurin inhibitors is recommended when the route of fluconazole administration is switched from i.v. to oral [5]. AUC indicates area under the curve.

Table 6. Other Azole Drug Interactions

Drug	Antifungal	Data Type	Effect	Recommendation
Busulfan	Flz	Nonrandomized SCT	Busulfan AUC increased	No action needed [11].
	Itz	Nonrandomized SCT	Busulfan clearance decreased	Avoid combination [11].
	Vrz	Theoretical (based on metabolism; no studies)	Busulfan clearance decreased	Consider starting Vrz after day 1 [11,13].
Calcium channel blockers	Itz	Randomized healthy volunteers	Felodipine AUC increased	Decrease felodipine dosage [108].
	Flz, Vrz, Psz	In vitro	Felodipine AUC increased	Monitor blood pressure.
Dexamethasone	Itz	Randomized healthy volunteers	Dexamethasone AUC increased	Monitor for toxicity [83].
Estrogens	Vrz	Nonrandomized healthy volunteers	Vrz and estrogen AUC increased	Monitor for Vrz toxicity [111].
	Flz	Randomized healthy volunteers	Estrogen AUC increased	No action needed [104].
Fentanyl/oxycodone	Flz, Vrz	Randomized healthy volunteers	Fentanyl AUC increased	Monitor for sedation [100].
Glipizide/glimepiride	Flz	Randomized healthy volunteers	Glimepiride AUC increased	Decrease glimepiride dose [103].
Methadone	Vrz	Randomized patients taking methadone	Methadone AUC increased	Monitor for methadone toxicity, QT-interval prolongation [110].
	Flz	Randomized patients taking methadone	Methadone AUC increased	Monitor for methadone toxicity, QT-interval prolongation [98].
Phenytoin	Psz	Nonrandomized volunteers	Psz AUC decreased	Avoid combination [114].
	Vrz	Randomized volunteers	Vrz AUC decreased; phenytoin AUC increased	Increase Vrz maintenance dose to 400 mg twice daily [109].
	Flz	Randomized volunteers	Phenytoin AUC increased	Monitor for phenytoin toxicity [99].
PPIs	Itz	Nonrandomized volunteers	Itz and omeprazole AUC increased	Do not use Itz capsules; solution okay [107].
	Vrz/Flz	Randomized/nonrandomized volunteers	Both AUC increased	No clinically relevant effect; start with low-dose PPI [102].
Statins	Itz/Psz	Randomized volunteers	Statin AUC increased	Avoid combination [115].
	Flz	Randomized volunteers	Statin AUC increased	Start low-dose statin [101].
	Vrz	In vitro	Statin AUC increased	Monitor for statin toxicity [112].
TKIs	Vrz/Psz	In vitro	TKI metabolism decreased	Avoid use with dasatinib/nilotinib, which also increases the risk of QT-interval prolongation; decrease dose if necessary. If using with imatinib, consider using lowest dose and closely follow for toxicity [43].

Flz indicates fluconazole; Itz, itraconazole; Psz, posaconazole; Vrz, voriconazole; PK, pharmacokinetic studies; CR, case reports.

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