MAJOR DRUG INTERACTIONS WITH CYCLOSPORINE AND TACROLIMUS

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Major drug interactions with cyclosporine (CsA) and tacrolimus (TAC):[1,2]

↑↑ Increased immunosuppressant concentration ↓↓ Decreased immunosuppressant concentration

Interacting class	Interacting agents	Effect(s)	Management suggestions
Anticonvulsants	Carbamazepine, pentobarbital, phenobarbital, phenytoin, primodone	↓↓ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration. Effect of CYP3A4 induction may occur over weeks.
Antimicrobials			
Antifungals	Fluconazole, itraconazole, ketoconazole (oral), posaconazole, voriconazole	↑↑ CsA or TAC concentration Additive QTc prolongation due to fluconazole or voriconazole with TAC	Closely monitor CsA or TAC serum concentration. The following empiric initial dose adjustments may be considered. For TAC: • decrease dose by 66% if initiating posaconazole or voriconazole, or by 40% if initiating fluconazole ≥ 200 mg/day For CsA: • decrease dose by 50% if initiating voriconazole, or by 25% if initiating posaconazole or fluconazole ≥ 200 mg/day.
Antimalarials	Mefloquine, quinine, quinidine	↑ CsA or TAC concentration Additive QTc prolongation due to tacrolimus with antimalarials	Closely monitor CsA or TAC serum concentration. Monitor for QTc prolongation if antimalarial treatment must be initiated in a patient receiving tacrolimus.
Antimycobacterial	Rifabutin, rifampin	↓↓ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration.
HIV and hepatitis C virus (HCV) antiretrovirals	Atazanavir, cobicistat, darunavir, delavirdine, fosamprenavir, indinavir, lopinavir-ritonavir, nelfinavir, ritonavir, saquinavir, tipranavir	↑↑ CsA or TAC concentration CsA may increase protease inhibitor concentrations	Closely monitor CsA or TAC serum concentration. If used with CsA, monitor protease inhibitor(s) for toxicity and serum concentrations where available. Early consultation with HIV/HCV infectious diseases specialist is recommended.
	Efavirenz, etravirine, nevirapine, tipranavir	↓↓ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration.
Macrolide antibiotics	Clarithromycin, erythromycin	↑↑ CsA or TAC concentration	Consider substituting a noninteracting antibiotic. Azithromycin and spiramycin are less likely to interact.

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Other anti-infectives	Chloramphenicol, levofloxacin, metronidazole, norfloxacin (with CsA), tetracycline, tigecycline	↑ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration.
Antineoplastic	Bicalutamide, nilotinib, sunitinib, tamoxifen, vandetanib, vemurafenib	↑ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration.
	Antineoplastic agents that are dependent upon CYP3A4 and/or P-gp for metabolism (e.g. doxorubicin, vinblastine)	CsA, and to a lesser degree TAC, may ↑ antineoplastic concentrations. Doxorubicin or vinblastine may ↓ CsA or TAC concentration	Monitor antineoplastic for exaggerated toxicity and monitor CsA or TAC serum concentration when used with doxorubicin or vinblastine.
	Crizotinib	↑ CsA or TAC concentration Increased QTc prolongation with TAC	Closely monitor CsA or TAC serum concentration. Avoid crizotinib with TAC or monitor for QTc prolongation.
Benzodiazepines	Alprazolam, clonazepam, diazepam, flurazepam, midazolam, triazolam	↑ benzodiazepine concentration with CsA	Monitor benzodiazepine effect to determine whether dose alteration needed.
Cardiovascular			
Antiarrhythmics	Amiodarone, dronedarone, lidocaine (systemic), quinidine	↑ CsA or TAC concentration Additive QTc prolongation with TAC	Closely monitor CsA or TAC serum concentration. Avoid QTc prolonging agents with TAC or closely monitor for QTc prolongation.
Anticoagulants (direct thrombin inhibitors and direct factor Xa inhibitors)	Apixaban, dabigatran, rivaroxaban	↑ anticoagulant concentration	Monitor for signs of excessive anticoagulation. **Avoid in patients receiving CsA or TAC with renal insufficiency (CrCl < 50 mL/min).**
Calcium channel blockers (CCB)	Diltiazem, verapamil	↑ ↑ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration.
	Amlodipine, felodipine, nifedipine	↑ ↑ TAC concentration	Closely monitor TAC serum concentration.
	Amlodipine, felodipine, nifedipine, nimodipine	↑ dihydropyridine CCB concentration with CsA	Monitor for exaggerated dihydropyridine CCB effects.

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HMG-CoA reductase inhibitors ("statins")	Atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	↑ statin concentration and risk of statin toxicity including myotoxicity with CsA TAC does not appear to alter atorvastatin concentrations in one pK study. There is one case report associating TAC and simvastatin usage with rhabdomyolysis.	**Avoid simvastatin.** Fluvastatin and pravastatin may have a lower risk of interaction. Avoid using maximum doses of statins as the statin blood levels are likely higher than expected from the dose.
Other cardiovascular	Carvedilol, dipyridamole, propranolol, reserpine	↑ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration. TAC is less likely to be altered than CsA.
Dietary	Grapefruit juice and grapefruit	↑ CsA or TAC concentration	Avoid grapefruit juice and grapefruit with CsA or TAC.
Gastrointestinal	Aprepitant, cimetidine, fosaprepitant	↑ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration
	Metoclopramide	↑ CsA or TAC concentration	
	Octreotide	↑ CsA (orally administered) Additive QTc prolongation with TAC	CsA microemulsion may be less likely to interact with octreotide.
	Orlistat	↓↓ CsA concentration	Closely monitor CsA serum concentration
	Omeprazole, lansoprazole	↑ TAC concentration	Pantoprazole and rabeprazole are less likely to interact.
Glucocorticoids and anti-gout			
Anti-gout	Allopurinol	↑↑ CsA concentration. The mechanism is unknown.	Closely monitor CsA serum concentration
	Colchicine	↑ colchicine toxicity. Toxic effects more pronounced with renal and/or hepatic insufficiency.	Monitor for toxicity and consider dose reduction if co-administration is unavoidable. For patients with normal renal and hepatic function, the following dose reductions are suggested: **acute gout**: 0.6 mg once followed by 0.3 mg one hour later. Do not repeat before 72 hours. **Gout prophylaxis**: reduce dose by 50%; double interval.
Herbs	St. Johns wort	↓↓ CsA or TAC concentration	Avoid St. John's wort with CsA or TAC.
	Schisandra	↑ TAC concentration	Avoid Schisandra with CsA or TAC.
Hormones	Estrogen preparations	↑ CsA concentration	Closely monitor CsA serum concentration
	Testosterone preparations (including danazol, methyltestosterone, testosterone)	↑ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration if concurrent use cannot be avoided.

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Hypnotic (also see benzodiazepines above)	zopiclone, zolpidem	↑ in hypnotic concentration with CsA	Monitor hypnotic effect to determine whether dose alteration is needed.
Hypoglycemic	Sulfonylureas including gliclazide, glimepiride, glyburide	↑ CsA concentration	Monitor CsA concentrations closely.
Immunosuppressant	Cyclosporine (CsA)	Increased risk of serious renal, hematologic, and other toxicities in combination with sirolimus ↓↓ mycophenolate concentration ↑↑ everolimus concentration ↑↑ sirolimus (with cyclosporine microemulsion)	Alteration of mycophenolate dosing is usually required when CsA is initiated, stopped, or added. When used with everolimus, reduction of CsA dose and target concentration is generally necessary. It is suggested that oral doses of sirolimus be administered four hours after cyclosporine doses.
	Tacrolimus (TAC)	Increased risk of serious renal, hematologic, or other toxicities with sirolimus ↑ everolimus concentration	Avoid concomitant use with sirolimus. If everolimus is used with TAC, closely monitor everolimus serum concentrations.
Psychiatry	Desipramine, haloperidol, fluoxetine, fluvoxamine, sertraline, trazodone	↑ CsA or TAC concentration	Consider antidepressants that do not interact; closely monitor CsA or TAC serum concentration if used.
	Pimozide	Elevated pimozide level and/or increased QTc prolongation	Avoid use of pimozide due to increased risk of cardiotoxicity.
Other	Bosentan	↓↓ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration.
	Cinacalcet	↓ CsA or TAC concentration	
	Sevelamer	↓ TAC concentration ↓↓ CsA concentration	

References

1. Major drug interactions with immunosuppressants: Lexi-interact 1978-2016
2. Baxter K, Baxter P, Claire, L. Immunosuppressant monograph: Stockley's drug interactions 10th ed. 2013