SUPPORTING EVIDENCE DOCUMENT FOR THE BCPRA CNI PROTOCOL FOR MN

BCRenal
an agency of the Provincial Health Services Authority

Objective

The purpose of the calcineurin inhibitor (CNI) protocol is to facilitate prescribing of cyclosporine and tacrolimus for the treatment of membranous nephropathy. This document summarizes the scientific evidence supporting the recommendations found in the CNI protocol.

1. Cyclosporine

Cyclosporine has been studied for the treatment of idiopathic membranous nephropathy since the late 1980's,[1-8] but the first prospective randomized controlled trial wasn't published until 1995 by Cattran et al.[7] This was a small study where 8 patients with progressive membranous nephropathy were randomized to cyclosporine and 8 patients were randomized to placebo. At 12 months, 88% of patients receiving cyclosporine demonstrated a slowing in rate of kidney function decline compared to 23% receiving placebo ($p < 0.02$). In addition 50% of patients receiving cyclosporine had a 50% reduction in proteinuria from baseline compared to zero patients receiving placebo.

In a second study in patients with steroid-resistant membranous nephropathy by Cattran et al.,[9] 75% of patients who received cyclosporine in combination with prednisone achieved remission at 6 months compared to 22% with placebo plus prednisone ($p < 0.01$). The relapse rate at 12 months was 43% in the cyclosporine group and 40% in the placebo group.

In 2006 Alexopoulos et al.[10] published a prospective observational study comparing cyclosporine monotherapy to cyclosporine plus prednisolone. Patients who received cyclosporine monotherapy had a history of gastrointestinal bleeding, peptic ulcer, significant osteoporosis, mild or borderline hyperglycemia, cataract, gastric intolerance and reluctance to receive corticosteroids. Remission rates were similar at 12 months (83% vs. 85% with monotherapy). After 12 months, cyclosporine was tapered to a maintenance dose of 1 to 1.5 mg/kg/day in both groups. During this period 15% of patients in the combination group relapsed compared to 47% in the monotherapy group ($p < 0.05$). However, cyclosporine trough levels were subtherapeutic in the monotherapy group (72 ± 48 ng/ml vs. 194 ± 80 ng/ml, $p < 0.03$), suggesting this to be the cause of the higher relapse rate.

2. Tacrolimus

Currently there are two prospective randomized multi-center studies evaluating tacrolimus for the treatment of idiopathic membranous nephropathy. The first study was published in 2007 by Praga et al.[11] who demonstrated a 72% remission rate at 12 months compared to 22% with no treatment; then after another 6 months of tapering tacrolimus, the remission rate increased to 76% (compared to 30% with no treatment). However after withdrawal was completed at 18 months, the relapse rate increased to 47%, which is comparable to the high relapse rates found in other calcineurin inhibitor studies.[9,10] This suggests calcineurin inhibitors do not provide a cure in many patients and that long-term therapy may be required.

The second study was published in 2010 by Chen et al.[12] who compared tacrolimus to oral cyclophosphamide both in combination with prednisone. The remission rate at 6 months was greater in the tacrolimus group (85 vs. 65%, $p < 0.05$) but was no different by month 12 (79 vs. 69%, $p > 0.05$). Three months after treatment was withdrawn, relapses rates were the same (15%).

3. Duration of calcineurin inhibitor treatment

The duration of treatment in calcineurin inhibitor studies were variable but many continued full treatment doses for 12 months.[7,10,11] After

remission is achieved, the relapse rate is high (up to 47%) if calcineurin inhibitors are stopped abruptly. This suggests calcineurin inhibitors do not provide a cure in many patients and long-term therapy may be required, especially in patients who only achieve partial remission (urine protein excretion less than 3.5 g/24 hours and a 50% reduction from baseline) rather than complete remission (urine protein excretion less than 0.3 g/24 hours). After 6 to 12 months, we suggest slowly tapering down the calcineurin inhibitor based on the patient's clinical remission status; some patients may require long-term therapy with a small individualized dose found to maintain remission during the taper.

4. Combination corticosteroid therapy

A higher relapse rate with cyclosporine monotherapy in the observational study by Alexopoulous et al.[10] is often cited as the rationale for combination therapy of calcineurin inhibitors with corticosteroids. However, the higher relapse rate found in the monotherapy group was likely the result of subtherapeutic serum levels rather than the addition of a corticosteroid.

Given prednisone monotherapy did not demonstrate a difference in remission rates compared to no treatment[13,14] and tacrolimus monotherapy in the Praga et al.[11] study showed a similar remission rate to cyclosporine combination therapy in the Cattran et al. studies,[7,9] it is hypothesized that corticosteroids do not add therapeutic value in the treatment of membranous nephropathy in combination with calcineurin inhibitors while subjecting the patient to risk of serious corticosteroid related side effects. The addition of a corticosteroid to a calcineurin inhibitor remains controversial and is not recommended in this protocol.

5. Laboratory monitoring

There is no systematic evidence evaluating different target serum trough levels of calcineurin inhibitors in the treatment of membranous nephropathy. Therefore the recommended serum trough levels in this protocol are guidelines only and dosing should be individualized based on patient tolerability and clinical response.

The estimated time to achieve a steady-state concentration of calcineurin inhibitors is between 5 to 10 days.[15] Therefore, weekly measurements of serum trough levels until they are stable is recommended, afterwards monthly measurements are reasonable, or as clinically indicated.

Other recommended laboratory measurements monitor adverse reactions that can be caused by calcineurin inhibitors. If serum creatinine increases by 30%, we suggest a calcineurin inhibitor dose reduction irrespective of serum trough level.

6. Drug interactions

Prescribers are reminded to be vigilant of the numerous drug interactions that exist with calcineurin inhibitors, particularly with drugs that inhibit or induce CYP 450 3A4 and/or P-gp. The following table summarizes major drug interactions only; it is not a complete list of all possible interactions.

Major drug interactions with cyclosporine (CsA) and tacrolimus (TAC):[16,17]

↑↑ 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 and for signs of toxicity (e.g. nephrotoxicity). 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.
Other anti-infectives	Chloramphenicol, levofloxacin, metronidazole, norfloxacin (with CsA), tetracycline, tigecycline	↑ CsA or TAC concentration	Closely monitor CsA or TAC serum concentration.

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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.
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 of rhabodmyolysis with TAC and simvastatin.	**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.

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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 serum concentration if concurrent use cannot be avoided.
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.

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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	

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