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Mary Pack Arthritis Program

ADVANCED THERAPEUTICS CLINIC

Guidelines for Monitoring Physicians

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TABLE OF CONTENTS

INTRODUCTION:

Cyclosporine and tacrolimus are powerful immunosuppressant drugs that have been extensively used for many years in the field of organ transplant. Both cyclosporine and tacrolimus display the pharmacodynamics property of activated T-cell suppression by inhibiting calcineurin. Cyclosporine/tacrolimus have been successfully adapted to treat patients with rheumatoid arthritis, as well as autoimmune diseases of the eyes, lungs, muscles, skin, and blood vessels.

Cyclosporine/tacrolimus is not a global immunosuppressant. Rather, they target specific cells selectively inhibiting the transcription of interleukin 2 (IL-2) and other cytokines in T-helper lymphocytes. Cyclosporine/tacrolimus lack clinically significant myelosuppression.

Cyclosporine/tacrolimus have been of benefit in controlling the extra articular features of rheumatoid arthritis, inflammatory ocular disease, interstitial lung disease, pyoderma, and psoriatic arthritis. As well, the medication has been helpful in managing psoriatic arthritis, polymyositis, and lupus (without nephritis).

Cyclosporine/tacrolimus is safe to use with patients who are hepatitis C positive.

Cyclosporine/tacrolimus is frequently used in combination with other disease modifying drugs and biologics to treat rheumatic disease. If used within established safety guidelines, cyclosporine/tacrolimus is a safe and effective drug for long-term therapy in inflammatory disease.

This booklet is prepared by the staff of the Advanced Therapeutics Clinic at the Mary Pack Arthritis Program in Vancouver, British Columbia. Each year the clinic treats about 100 patients throughout the province. The information contained in this booklet is based on evidence from clinical trials, research literature, and extensive experience working with patients in the clinic.

Selecting Patients for Therapy

a) Cyclosporine/tacrolimus is **contraindicated** in patients with:

i. abnormal kidney function
ii. uncontrolled hypertension
iii. malignancy within the last 5 years (except non-melanoma skin cancer such as basal cell carcinoma)
iv. uncontrolled infection
v. primary or secondary immunodeficiency excluding autoimmune disease
vi. hypersensitivity to cyclosporine/tacrolimus
vii. abnormal liver function (liver function test results that are more than twice the upper limit of normal)

b) Cyclosporine/tacrolimus is used **with caution** in patients:

i. with controlled hypertension
ii. over 65 years who are at greater risk for hypertension or renal insufficiency
iii. with a history of infections
iv. obese patients (dosing should be based on ideal body weight)
v. undergoing radiation therapy
vi. who are pregnant or contemplating pregnancy

c) Cyclosporine/tacrolimus have been successfully used to treat patients with:

i. rheumatoid arthritis
ii. psoriatic arthritis
iii. polymyositis/dermatomyositis
iv. vasculitis
    - polyarteritis nodosa
    - giant cell arteritis
    - Wegener's granulomatosis
    - Takayasu's arteritis
    - Churg-Strauss
    - Behçet's disease
    - Pyoderma gangrenosum
v. interstitial lung disease
vi. lupus (without nephritis)
vii. autoimmune eye disorders
    - corneal melt
    - scleritis
    - uveitis
    - birdshot retinochoroidopathy
viii. relapsing polychondritis
ix. some neurological diseases (myasthenia gravis)

Administering Cyclosporine

Cyclosporine is available in 25 mg, 50 mg, and 100 mg capsules, and a liquid suspension. It is administered twice a day, 12 hours apart. It can be taken with or without food.

The therapeutic dose of cyclosporine is determined by assessing the patient's ideal body weight, medical condition, blood work, and clinical response to the medication. There are two accepted methods for administering cyclosporine.

- **Titration**
  Over a 3-week period, the dose of cyclosporine is gradually increased from 2.5 mg/kg/day to 4 mg/kg/day. The dose can be started in exceptional circumstances at 5 mg/kg/day, but should never exceed that amount. Titration method best used for low body weight patients.

- **Standardization**
  Start cyclosporine at 50-100 mg b.i.d. This dose can be later adjusted based on the patient's response to the medication.

Administering Tacrolimus

Tacrolimus is available in 0.5 mg, 1 mg, and 5 mg capsules. The capsules are taken orally twice a day, 12 hours apart.

- **Titration**
  Over a one month period, the dose of tacrolimus is gradually increased from 0.5 mg to 2 mg b.i.d., maximum dosing is 5 mg b.i.d.

Table 1: Comparative Side Effects of Calcineurin Inhibitors
http://www.jimmunol.org/content/jimmunol/191/12/5785.full.pdf

Side Effects	Cyclosporine	Tacrolimus
Vasoconstriction	++	+
Fibrogenesis	++	+
Lower Serum Creatinine	-	+
Better graft survival	-	+
Diabetes	+	++
Tremor	+	++
Hirsutism	++	-
Gingival hyperplasia	++	+
Dyslipidemia	++	+

++ more pronounced side effects
+ less pronounced side effects
- no side effects

There is some evidence to suggest that grapefruit or pomelo may interfere with the absorption of cyclosporine/tacrolimus, due to metabolism in the liver and small intestine via the cytochrome p-450 pathway. Patients are advised not to eat grapefruit, tangelo, noni, or pomelo and/or juice while taking the medication. It is also advisable to avoid red wine and pomegranate juice.

See Table 2, for a brief summary of herbal extracts and their interactions with the metabolism of cyclosporine/tacrolimus.

Patients are encouraged to drink 1.5 liters of fluid a day while on cyclosporine/tacrolimus. Dehydration can impact renal function and lead to increased creatinine levels.

Patients may drink tea and coffee with cyclosporine/tacrolimus, but because of their caffeine content, the tea and coffee do not count as part of the 1.5 liters.

Although tacrolimus and cyclosporine share a similar mechanism of action, the side effect profile of these medications can be different.

Monitoring Cyclosporine/Tacrolimus

a. Clinical Assessment

Patients with rheumatoid arthritis should be assessed every three to six months for:

- joint count
- morning stiffness
- fatigue
- adverse events
- concomitant medications

Patients with autoimmune conditions such as vasculitis, myositis, or eye disorders will require monitoring parameters appropriate to the specific disease.

b. Clinical Response

A clinical response to cyclosporine/tacrolimus should appear within 3-4 months.

- If after 4 months the patient has a partial response to cyclosporine/tacrolimus, the addition of another immunosuppressant medication, such as Methotrexate, could be considered.
- If after 4 months there is no clinical response to the maximum dose, cyclosporine/tacrolimus should be discontinued.

c. Laboratory Monitoring

i) Baseline blood work:
- complete blood count (CBC), differential, platelets
- total bilirubin
- liver enzymes (AST, ALT, alkaline phosphatase, BUN, albumin)
- serum creatinine
- serum sodium, potassium, magnesium
- serum uric acid
- random blood sugar
- CRP
- Hep BsAg, Hep B core Ag, Hep BsAb
- Anti-hepatitis C
- HIV serology
- CK

ii) Monthly blood work:
- CBC, platelets
- AST, ALT, potassium, magnesium
- Serum creatinine, cyclosporine/tacrolimus trough level – 12 hours post dose
- CRP
- CK

Cyclosporine/tacrolimus levels are checked monthly for drug interaction or drug compliance.

Tacrolimus trough levels between 4-12 ug/L are considered acceptable readings for autoimmune disease. Cyclosporine trough levels between 75-340 ug/L are considered acceptable readings for autoimmune disease. (adapted from Vancouver General Hospital, Division of Clinical Chemistry, June 2017).

Table 2

Herbal Supplement or Extract	Effect of Interaction on CyA bioavailability	Mechanism of Interaction	Studies
St. John's Wort	Decreased	Hypericin: P-GP Hyperforin: induces intestinal and hepatic CYP3A4, CYP2B6 and P-GP	Human
Grapefruit juice	Increased (oral only)	Inhibits intestinal CYP3A4	Human
Ginger	Decreased	Reduces gastrointestinal motility	Animal
Cannabidiol	Increased	Inhibits hepatic CYP3A4	Animal
Chamomile	Increased	Inhibits CYP3A4	Human (case report)
Liquorice	Decreased (oral only)	Induced P-GP and CYP3A4	Animal
Scutellariae radix	Decreased (oral only)	Induces CYP3A4 and intestinal P-GP	Animal
Quercetin	Decreased (oral only)	Induces CPY3A4 and intestinal P-GP	Animal
Resveratrol	Increased (speculative)	Induces CPY3A4	Animal
Serenoa repens	Increased (speculative)	Potent inhibitor of CYP3A4, 2D6 and 2C9	In-vitro
Echinachea	Increased (speculative)	Possible inhibitor of CYP (data inconclusive)	In-vitro
Berberine	Increased	Inhibits CYP3A4 and intestinal P-GP	Human

Table 2 – Taken from J. Toxicology, Volume 2014 Colombo, D. Lunardon, L et al Cyclosporine and Herbal Supplement Interactions.
https://www.hindawi.com/journals/jt/2014/145325/

Key Questions With Elevated Creatinine Levels

1. Hydration: At least 1.5 liters of fluid daily and coffee and tea do not count.

2. Recent illnesses: Vomiting and diarrhea can lead to dehydration affecting clearance.

3. Any new medications, use of supplements or herbal remedies:
Consuming any of the foods on the interaction list, i.e. grapefruit (grapefruit compounds can last up to 72 hours in the body).

4. Drinking red wine, which can also affect levels.

5. Timing of the blood test.

6. Other nephrotoxins used along with these medications.

Orders As Outlined Through the Advanced Therapeutics Clinic

1. If creatinine value is less than 10 above threshold, repeat creatinine in one week and increase fluid intake.

2. If creatinine 10 or above the threshold, temporarily stop cyclosporine/tacrolimus, increase fluid intake and repeat creatinine in 1 week.

3. The restart dose depends on the duration of creatinine elevation and the response to temporary stoppage and will be decided by the rheumatologist in the clinic or the primary rheumatologist.

We advise regular follow ups with the specialist physicians (rheumatologists, ophthalmologists) if patients are off medications due to creatinine elevation to ensure there is no flare up of the disease.

Medication Interactions

a. Drugs to avoid when on cyclosporine/tacrolimus:

- New oral anti-coagulant drugs (rivaroxaban, dabigatran, apixaban, edoxaban)
- Colchicine
- Cyclophosphamide
- Chlorambucil
- Hydrochlorothiazide
- Tacrolimus
- Rifampin (anti-tuberculosis medication)
- Apotex/cimetidine (GI motility modifying drugs)

- HMG-CoA reductase (can cause rhabdomyolysis)
- Pravastatin
- Lovastatin
- Simvastatin (Zocor)
- Lipitor
- Lipidil
- Tracleer (bosentan)
- Multaq
- Micronor

Cholesterol-reducing medications such as Niacin, Questran, and Exetrol can be used with cyclosporine.

b. Drugs to use with caution when on cyclosporine/tacrolimus:

- Prednisone
- Anti-inflammatory medications (NSAIDs)
- Digoxin
- Anticoagulants (Coumadin, warfarin)
- Salicylates
- Calcium channel blockers
- Contraceptives
- Aldactone
- Furosemide
- Marijuana
- Statins (low dose Crestor, Pravachol, and Lescol are the safest statins with cyclosporine. Consider Ezetrol rather than a statin for cholesterol reduction).

c. Drugs to avoid if possible when on cyclosporine/tacrolimus (see Table 3 of antibiotics, antifungal and antivirals with calcineurin inhibitors)

- Clarithromycin
- Erythromycin
- Nafcillin
- Sulfamethoxazole
- Gentamicin, vancomycin, tobramycin
- Anti-fungal / anti-viral medications (ketoconazole, acyclovir metronidazole)
- Anti-convulsants / barbiturates

Caution: If you are unable to avoid the use of the above medications, hold the cyclosporine/tacrolimus until the acute treatment is finished. A rebound effect from being off cyclosporine/tacrolimus should not occur for 4 weeks after stopping the medication.

Table 3 – Common antibiotics and their compatibility with cyclosporine/tacrolimus. (Note: This is not a comprehensive list).

Antibiotic, Antifungal & Antiviral Compatibility With Cyclosporine & Tacrolimus

Antibiotics

Compatible	Non-Compatible	
Amoxicillin	Clarithromycin (Biaxin) *	}
Amoxi-clav	Gentamycin	}
Cefazolin (Ancef)	Tobramycin	} May increase CyA or
Cefiximine (Suprax)	Nafcillin	} tacro levels
Cefuroxime (Keflex)	Erythromycin	}
Cephalexin	Chloramphenicol	}
Ciprofloxacin (Cipro)		
Clindamycin		
Doxycycline	Sulfamethoxazole	} May decrease CyA or
Moxifloxacin	Sulfamethoxazole/Trimethoprim	} tacro levels
Nitrofurantoin (Macrobid)		Increase nephrotoxicity
Vancomycin		

a. Radiation and phototherapy (PUVA/UVB) should be avoided while taking cyclosporine/tacrolimus. There is an increased risk of skin cancer with their use and therefore sunscreen is recommended.

b. Over-the-counter medications such as cold remedies, pain medication, cough syrup, and vitamins **are not thought** to interact with cyclosporine/tacrolimus. It is advised to limit anti-inflammatory medications such as ibuprofen.

c. Information of herbal medications and their interactions with cyclosporine/tacrolimus is scarce. Limited studies suggest avoiding combining cyclosporine/tacrolimus with: St. John's wort, Echinacea, ginger, marijuana, chamomile, liquorice, goldenseal, scutellariae, radix, quercetin, serenoa repens, and berberine (see Table 2).

Antifungals

Oral forms not compatible with cyclosporine/tacrolimus.
Examples: fluconazole, ketoconazole.
Topical anti-fungal preparations are compatible with oral cyclosporine/tacrolimus.

Antivirals

Generally not used with cyclosporine/tacrolimus.
Those with active viral infections that require anti-viral treatment often advised to temporarily hold cyclosporine/tacrolimus (shingles).
Exception would be low dose anti-viral treatment to prevent herpes reactivation.

Managing Adverse Side Effects

The adverse side effects of cyclosporine/tacrolimus fall into three categories: major, minor and rare. All side effects are dose dependent and reversible. Most side effects can be managed or eliminated by stopping the medication or adjusting the dose.

a. Major Adverse Side Effects: Hypertension and Renal Function

i. *Hypertension*

Hypertension may develop or existing hypertension may worsen with cyclosporine/tacrolimus therapy. The patient's blood pressure should be checked once a week for the first month of therapy and once a month thereafter.

Hypertension in the context of cyclosporine/tacrolimus therapy, is defined as a systolic reading of >140 mm/Hg or a diastolic reading of >90 mm/Hg on two consecutive occasions over a one week period.

Strategies for Managing Hypertension

- Decrease the cyclosporine/tacrolimus dose for one week. If the blood pressure returns to normal, reinitiate the medication.

- If the dose reduction does not improve the blood pressure in one week, you may introduce an anti-hypertensive medication. Beta blockers (nadolol, metoprolol), calcium channel blockers (Adalat XL, Norvasc, felodipine or amlodipine), or ACE inhibitors (Ramipril) are possible choices.

- If you are unable to bring hypertension under control within one month, cyclosporine/tacrolimus therapy should be discontinued.

Caution:
Avoid the use of beta blockers in patients who have psoriatic arthritis or asthma. Beta blockers can exacerbate both conditions.

Diuretics are not recommended with cyclosporine/tacrolimus therapy. Avoid hydrochlorothiazide and potassium-sparing diuretics.

ii. *Renal Function*

Cyclosporine/tacrolimus may cause an increase in serum creatinine levels and may reduce the glomerular filtration rate (GFR).

Calculating target creatinine

A creatinine target is established for each patient by calculating a number 30% above the patient's creatinine level prior to initiating cyclosporine/tacrolimus therapy.

If the creatinine level is within 30% of the patient's creatinine prior to starting therapy and if the dose of cyclosporine/tacrolimus is kept below 5 mg/kg/day, there is virtually no risk of developing permanent cyclosporine/tacrolimus induced nephropathy or nephrotoxicity.

The duration and cumulative doses of cyclosporine/tacrolimus are not found to be risk factors for nephrotoxicity.

b. Minor Adverse Side Effects

Minor adverse side effects are usually self-limiting. They do not typically require treatment and are reversible when the dose of cyclosporine/tacrolimus is reduced or the treatment is discontinued.

- nausea, bloating, loose stools, abdominal cramps
- slight trembling of the hands
- tingling in the fingers, toes, lips
- muscle or joint discomfort, cramping
- sensitivity to heat and cold
- mild headaches
- increased growth of fine hairs on the body
- tender or swollen gums
- acne, oily skin
- fatigue
- edema in the legs or ankles
- mild depression or mood swings

Laboratory abnormalities can include hyperuricemia, hyperkalemia, hypomagnesemia, hyperlipidemia, and hyperglycemia. These conditions are rare, mild, and seldom require treatment. Significant tremulousness, weakness,

and cardiac risk factors should prompt evaluation of magnesium levels and hyperlipidemia respectively.

c. Rare Adverse Side Effects

Lymphoma:

Although very rare, lymphomas have occurred. These rare cases appear to be dose related. Patients taking cyclosporine/tacrolimus for autoimmune disease are on a very low dose of the medication. If patients follow their doctor's instructions, the risk of lymphoma appears to be virtually non-existent. If a malignancy, other than a non-melanoma skin cancer is detected, cyclosporine/tacrolimus should be stopped. The drug can be restarted after careful consultation with the patient and the oncologist.

Liver Function:

On rare occasions, cyclosporine/tacrolimus can affect the liver. Blood tests are performed each month to check liver function. If abnormalities occur, cyclosporine/tacrolimus is discontinued. The liver function will return to normal once the medication has been stopped.

Hepatitis B/C:

International standards require that a patient starting cyclosporine/tacrolimus therapy be tested for hepatitis B and C. Although there is significant evidence to suggest that cyclosporine/tacrolimus can exacerbate hepatitis B, it appears to be safe to treat patients who are hepatitis C positive.

Concomitant Therapy

a. Surgery

Patients should stop cyclosporine/tacrolimus 24 hours prior to surgery. Cyclosporine/tacrolimus may be restarted when the patient is eating and drinking normally. Cyclosporine/tacrolimus does not impact negatively on the healing process.

b. Active Infections

The body maintains its capacity to fight infection while on cyclosporine/tacrolimus therapy. Patients with minor infections can continue to take the medication. Patients with serious infections are advised to stop cyclosporine/tacrolimus until the infection has cleared.

Patients should temporarily hold cyclosporine/tacrolimus if they are ill with a condition that interferes with fluid balance (nausea, vomiting, diarrhea).

Shingles with active lesions is cause to temporarily stop cyclosporine/tacrolimus.

Most antibiotics impact the absorption level of cyclosporine/tacrolimus. You can choose to hold cyclosporine/tacrolimus while your patient takes antibiotics (see Table 3).

c. Pregnancy

Information on pregnancy and cyclosporine/tacrolimus therapy is limited to transplant patients. Available research data suggests the risk for mothers with autoimmune disease is similar to that of transplant patients. Birth deformities have not been connected to cyclosporine/tacrolimus therapy and pregnancy. The fetus is at greater risk of premature delivery and low birth weight. Most patients who become pregnant continue cyclosporine/tacrolimus therapy under the direction of a high risk pregnancy clinic.

Males taking cyclosporine/tacrolimus have fathered normal children.

d. Breastfeeding

Cyclosporine/tacrolimus is transferred into the breast milk of lactating mothers. Mothers are advised **not** to breast feed their babies while on cyclosporine/tacrolimus.

e. Vaccines

Flu shots, pneumonia vaccines, and on consultation with the rheumatologist, Shingrix vaccine are recommended for patients on cyclosporine/tacrolimus. Vaccines may be less effective. The use of attenuated vaccines should be avoided.

Pharmacare Coverage

Special Authority application for cyclosporine coverage is not necessary if prescribed by a rheumatologist, dermatologist, nephrologist, or ophthalmologist under certain diagnoses. Pharmacare will cover 75% of the cost of the medication after the patient has reached his/her deductible. Most extended benefits cover 80-100% of the remaining cost.

Neoral brand cyclosporine requires a Special Authority.

When disease symptoms persist and/or trough cyclosporine levels are low with adequate dosing of cyclosporine, consider a trial of Neoral.

Neoral is thought to be more consistently absorbed than the generic brand. Neoral is highly recommended for vision or breath threatening inflammatory disease.

Tacrolimus requires Special Authority coverage.

Websites for Journal Articles

Cyclosporine and Herbal Supplement Interactions
https://www.hindawi.com/journals/jt/2014/145325/

Tacrolimus, a Calcineurin Inhibitor, Overcomes Treatment Unresponsiveness Medicated by P-glycoprotein on Lymphocytes in Refractory Rheumatoid Arthritis
http://www.jrheum.org/content/jrheum/early/2010/01/11/jrheum.090048.full.pdf

Calcineurin Inhibitors: 40 Years Later, Can't Live Without…
http://www.jimmunol.org/content/191/12/5785

UpToDate: Treatment of Recurrent and Resistant Dermatomyositis and Polymyositis in Adults
http://www.uptodate.com/contents/interstitial-lung-disease-in-dermatomyositis-and-polymyositis-treatment?search=treatment%20of%20interstitial%20lung%20disease&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

IgG4-Related Disease
https://www.nejm.org/doi/pdf/10.1056/NEJMra1104650

Electrolyte and Acid-Base Disturbances Induced by Calcineurin Inhibitors
https://www.researchgate.net/publication/259883865/download

Postoperative Corneal Melt Treatment and Management
https://emedicine.medscape.com/article/1193347-treatment

UpToDate: Ocular Manifestations of Rheumatoid Arthritis
https://www.uptodate.com/contents/ocular-manifestations-of-rheumatoid-arthritis

Additional Resources:

The efficacy of calcineurin inhibitors for the treatment of interstitial lung disease associated with polymyositis/dermatomyositis Lupus 2015 24, 3-9