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Mary Pack Arthritis Program

CYCLOSPORINE CLINIC

Guidelines For Monitoring Physicians

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CONTENTS

INTRODUCTION:

Cyclosporine is a powerful immunosuppressant drug that has been extensively used for many years in the field of organ transplant. Since 1979, cyclosporine has been successfully adapted to treat patients with rheumatoid arthritis, as well as autoimmune diseases of the eyes, lungs, muscles, skin and blood vessels.

Cyclosporine is not a global immunosuppressant. Rather, it targets specific cells selectively inhibiting the transcription of interleukin 2 (IL-2) and other cytokins in T-helper lymphocytes. Cyclosporine lacks clinically significant myelosuppression.

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

Cyclosporine is frequently used in combination with other disease modifying drugs and biologics to treat rheumatic disease. Research literature suggests that cyclosporine is especially effective when combined with Methotrexate in controlling autoimmune disease. If used within established safety guidelines, cyclosporine is a safe and effective drug for long-term therapy in inflammatory disease.

This booklet is prepared by the staff of the Cyclosporine Clinic at the Mary Pack Arthritis Centre in Vancouver, British Columbia. It is offered as a guide to assist physicians who wish to use this medication in their private practices. Each year the clinic treats about 100 patients throughout the province. The information contained in the booklet is based on evidence from clinical trials, research literature, and 25 years experience working with patients in the clinic.

1) Selecting Patients for Cyclosporine Therapy

i) Cyclosporine is **contraindicated** in patients with:

a) abnormal kidney function
b) uncontrolled hypertension
c) malignancy within the last 5 years (except non-melanoma skin cancer such as basal cell carcinoma)
d) uncontrolled infection
e) primary or secondary immunodeficiency excluding autoimmune disease
f) hypersensitivity to cyclosporine
g) abnormal liver function (liver function test results that are more than twice the upper limit of normal)
h) gout (serious drug interaction with colchine)

ii) Cyclosporine is used **with caution** in patients:

a) with controlled hypertension
b) over 65 years who are at greater risk for hypertension or renal insufficiency
c) with a history of infections
d) obese patients (dosing should be based on ideal body weight)
e) undergoing radiation therapy
f) who are pregnant or contemplating pregnancy

iii) Cyclosporine has been **successfully used** to treat patients with:

a) rheumatoid arthritis
b) psoriatic arthritis
c) polymyositis / dermatomyositis
d) vasculitis
    polyarteritis nodosa
    giant cell arteritis
    Wegener's granulomatosis
    Takayasu's arteritis
    Churg-Strauss
    Behcet's disease
    Pyoderma gangrenosum
e) interstitial lung disease
f) lupus (without nephritis)
g) autoimmune eye disorders
(corneal melt / scleritis / uveitis / birdshot retinochoroidopathy)
h) relapsing polychondritis

2) 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. There is some evidence to suggest that grapefruit or pomello may interfere with the absorption of cyclosporine. Patients are advised **not to** eat grapefruit or pomello and/or juice **while taking** the medication. No other juices cause this problem.

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

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

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.

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

3) Monitoring Cyclosporine

i) Clinical Assessment

Patients with rheumatoid arthritis should be assessed every three 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.

ii) Clinical Response

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

- If after 4 months the patient has a partial response to cyclosporine, 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 should be discontinued.

iii) Laboratory Monitoring

a) Baseline Blood Work:

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

b) Monthly Blood Work:

CBC, platelets
AST
Serum creatinine
Serum magnesium
CRP
CK

Cyclosporine levels are not routinely checked in the Cyclosporine Clinic because the levels in autoimmune therapy do not necessarily predict efficiency or toxicity. The levels are more useful in the management of transplant patients.

Cyclosporine levels are checked periodically for drug interaction or drug compliance. Cyclosporine trough levels between 50-200 ug/L are considered acceptable readings for autoimmune disease.

4) Managing Adverse Side Effects of Cyclosporine

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

i) Major Adverse Side Effects: Hypertension and Renal Function

a) Hypertension

Hypertension may develop or existing hypertension may worsen with cyclosporine 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 therapy, is defined as a systolic reading of >140 mm/Hg or a diastolic reading of >95 mm/Hg on two consecutive occasions over a one week period.

Strategies for Managing Hypertension

- Decrease the cyclosporine dose for one week. If the blood pressure returns to normal, reinitiate the medication.
- If dose reduction does not improve the blood pressure in one week, you may introduce an anti-hypertensive medication. Beta blockers (nadolol), calcium channel blockers (Adalat XL, Norvasc), or ace inhibitors (captopril, accupril, altace) are possible choices.
- If you are unable to bring hypertension under control within one month, cyclosporine 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 therapy. Avoid hydrochlorothiazide if possible. Furosemide or aldactone are better diuretic alternatives.

b) Renal Function

Cyclosporine may cause an increase in serum creatinine levels and may reduce the glomerular filtration rate (GFR). A creatinine target is established for each patient by calculating a number 30% above the patient's creatinine level prior to initiating cyclosporine therapy.

If the creatinine level is within 30% of the patient's creatinine prior to starting therapy and if the dose of cyclosporine is kept below 5 mg/kg/day, there is

virtually no risk of developing permanent cyclosporine induced nephropathy or nephrotoxicity.

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

Serum creatinines are monitored every week for the first 2 weeks of therapy and every month thereafter.

Strategies for Managing Elevated Creatinine

If the serum creatinine rises beyond the target range, first check with the patient that:

- he/she does not have an acute illness
- he/she is drinking 1.5 litres of fluid a day
- he/she has not added any new medications that may interfere with the absorption of cyclosporine.

If the creatinine is above the target range, hold the cyclosporine and repeat the creatinine weekly until it is back within target range. Restart cyclosporine at a lower dose and gradually increase the dose back to the therapeutic level.

If the creatinine remains above the target range for more than a month, discontinue cyclosporine therapy.

ii) 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 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, hypomagnesuria, 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.

iii) Rare Adverse Side Effects

a) ***Lymphoma*:** Although very rare, lymphomas have occurred. These rare cases appear to be dose related. Patients taking cyclosporine 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 should be stopped. The drug can be restarted after careful consultation with the patient and the oncologist.

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

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

5) Medication Interactions

i) Drugs **to avoid** when on cyclosporine:

Colchicine
Cyclophosphamide
Chlorambucil
Hydrochlorothiazide
Tacrolimus
Rifampin (anti-tuberulosis 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, Qestran and Ezetrol can be used with cyclosporine.

ii) Drugs to use **with caution** when on cyclosporine:

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

iii) Drugs to **avoid if possible** when on cyclosporine:

Clarithromycin
Erythromycin, Moxifloxacin
Doxycycline
Ciprofloxacin
Gentamicin, vancomycin
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 until the acute treatment is finished. A rebound effect from being off cyclosporine should not occur for 4 weeks after stopping the medication.

iv) Radiation and phototherapy (UVB/UVA) should be avoided while taking cyclosporine.

v) Over-the-counter medications such as cold remedies, pain medication, cough syrup and vitamins are not thought to interact with cyclosporine.

vi) Information of herbal medications and their interactions with cyclosporine is scarce. There is some evidence to suggest that St. John's Wort can decrease the concentration of cyclosporine in the bloodstream. Echinacea should be avoided since it increases cyclosporine levels.

6) Concomitant Therapy

i) <u>Surgery</u>

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

ii) Active Infections

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

Most antibiotics impact on the absorption level of cyclosporine. You can choose to hold cyclosporine while your patient takes antibiotics.

iii) Pregnancy

Information on pregnancy and cyclosporine 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 therapy and pregnancy. The fetus is at greater risk of premature delivery and low birth weight. Most patients who become pregnant continue cyclosporine therapy under the direction of a high risk pregnancy clinic.

Males taking cyclosporine have fathered normal children.

iv) Breastfeeding

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

v) Vaccines

Flu shots and pneumovax injections are recommended for patients on cyclosporine. Vaccines may be less effective. The use of attenuated vaccines should be avoided.

7) Pharmacare Coverage

Special Authority application for cyclosporine coverage is not necessary if prescribed by a rheumatologist, dermatologist, nephrologist or ophthalmologist under certain diagnosis. 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.

8) Blood Pressure Cuffs

Patients may find it convenient to purchase a blood pressure machine from their local drug store or medical supply store. With a doctor's prescription, extended benefits will cover most of the cost of the blood pressure machine or it may be deducted from your income tax.