Cyclosporine in the Treatment of Psoriasis

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The efficacy of cyclosporine is well documented in multiple clinical trials. Patients with severe psoriasis who require systemic treatment should be considered for this therapeutic agent. The need for both a careful evaluation prior to therapy and strict monitoring of the patient cannot be over emphasized because untreated hypertension, renal dysfunction, and other disorders may lead to serious, nonreversible morbidity. Physicians are encouraged to follow the published guidelines for controlling psoriasis in their patients and lowering the risk of potential drug toxicity.

Psoriasis is a common skin disorder that affects 2% of the population. Although psoriasis can begin in childhood, most patients experience onset after age 25. The majority of patients with psoriasis have localized disease, but approximately 10% have severe psoriasis that requires systemic therapy. The options for systemic treatment include methotrexate, acitretin, and cyclosporine. Although introduced more than 10 years ago in Canada, cyclosporine is now gaining greater acceptance as first-line therapy for psoriasis that requires systemic therapy. This drug is very effective in the treatment of severe psoriasis,[1-4] and significant improvement can be seen with its use after 4 to 6 weeks. Cyclosporine also has predictable efficacy and, for the most part, reversible side effects. To aid physicians in the proper use of cyclosporine, the Canadian, United States, and international guidelines should be followed.[5-7] Neoral® (cyclosporine), the microemulsion formulation of cyclosporine, may have improved efficacy[8] and a better safety profile because of its more predictable and stable absorption.[9] Other advances include the use of intermittent therapy[10,11] and combination therapy.[12] Through the use of cyclosporine, patients have the potential of long-term control of their psoriasis with predictable and, for the most part, reversible adverse events. These results, however, can only be achieved if the physician is knowledgeable in the use of cyclosporine and follows the treatment guidelines.

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Neoral (Cyclosporine)

Cyclosporine is now marketed as a microemulsion preconcentrate known as Neoral. The efficacy of cyclosporine is well documented in multiple clinical trials,[1-4] and this new formulation has shown improvement in efficacy[8] and predictable and rapid absorption with reproducible pharmacokinetics[9] that are not significantly influenced by food or bile. Recent studies have shown that, on average, the Neoral formulation exhibits a 29% higher bioavailability with a maximum concentration that is 59% higher and that occurs 1 hour earlier than the Sandimmune® (cyclosporine) formulation.[8] The Neoral formulation also has been shown to have less intra- and interpatient variability.[9]

Patient Selection

Patients with severe psoriasis who require systemic therapy should be considered for Neoral treatment. Contraindications for the use of cyclosporine include a previous history of cancer (with the exception of basal cell carcinoma), immunodeficiency of any type, premalignant conditions, severe liver disease, abnormal renal function, uncontrolled hypertension, or serious active infection. Experience with this drug in pregnancy is limited; if possible, pregnancy should be avoided.

How to Use Neoral: Initial Evaluation

Prior to initiating a patient on Neoral therapy, physicians should obtain a detailed medication history and perform a thorough physical and dermatologic examination. Special attention should be paid to malignant or premalignant conditions of the skin, mucosa, and lymph nodes. Blood pressure should be taken on 2 occasions within 2 weeks of treatment to establish

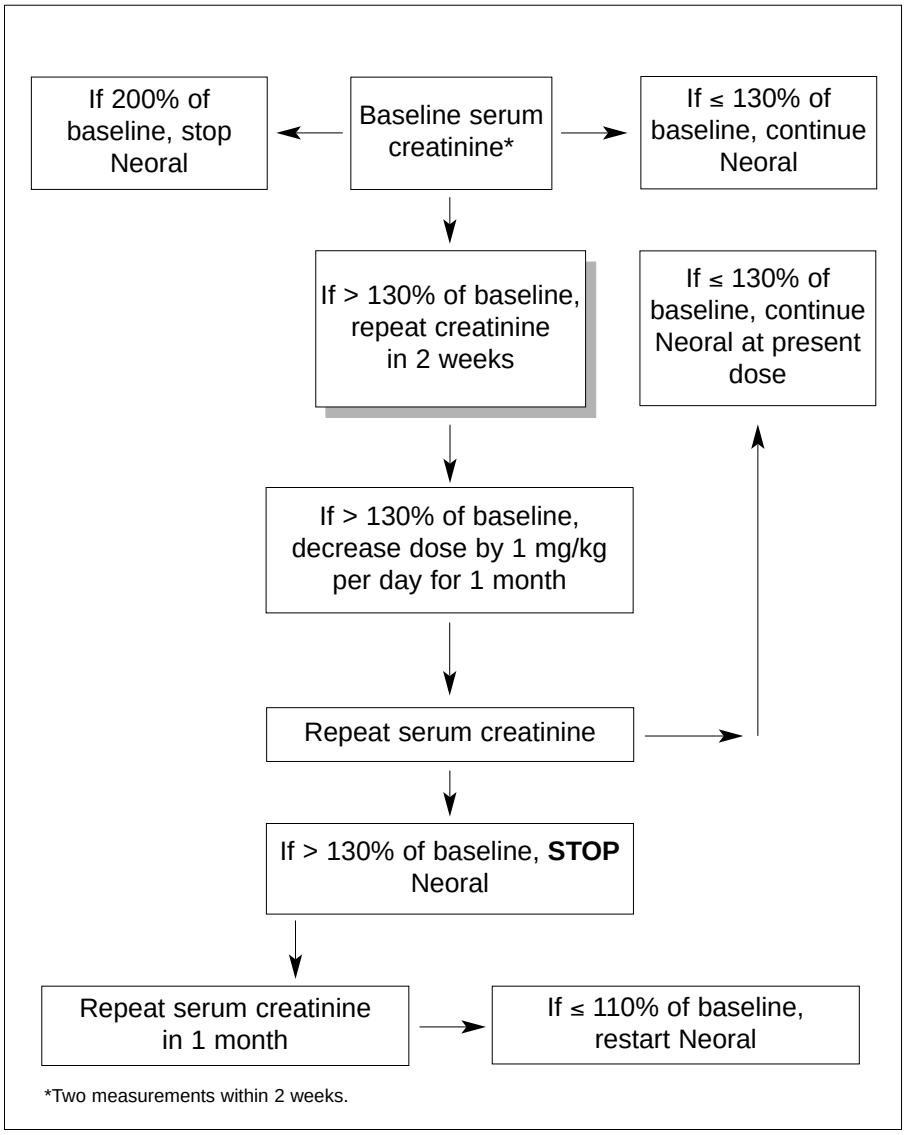

FIGURE 1. Guidelines for monitoring serum creatinine levels.

a baseline. Patients should also undergo routine examinations recommended for their age groups with respect to cervical, breast, and prostate malignancy. A list of all medications, including changes in medications or new medications, should be given to the physician to avoid potential drug interactions (Table I). These interactions are classified as substantiated, suspected, or potential and fall into 3 categories: (1) drugs that increase serum concentration of cyclosporine; (2) drugs that decrease the serum concentration of cyclosporine; and (3) drugs that may have additive nephrotoxicity. Other interactions also have been observed.

Laboratory Investigations

Measurements of renal function are of vital importance, with blood urea nitrogen (BUN) and creatinine being the most useful predictors of renal function. On 2 separate occasions, BUN and creatinine levels should be measured after a 12-hour fast within 2 weeks of initiation of therapy, and they also should be tested every 2 weeks for the first 3 months and every 2 months thereafter. Patients who receive cyclosporine in doses of 2.5 mg/kg per day or higher should have monthly creatinine tests.[5] Complete blood count differentials should be done at baseline and every 3 months, and a lipid profile should be done at baseline and every 6 to 12 months if the baseline is abnormal. If creatinine levels rise above 30% of baseline, they should be assessed more frequently (Figure 1).

Neoral Dosage

Therapeutic options for Neoral include continuous intermittent therapy or combination therapy. The suggested initial dosage is 2.5 mg/kg per day given in

2 divided doses 12 hours apart. If that dosage does not provide reasonable improvement after 1 month, it should be increased by 0.5 to 1.0 mg/kg per day at monthly intervals, with the maximum dosage being 5.0 mg/kg per day. In continuous therapy, the lowest effective dosage is maintained to keep the psoriasis under acceptable control. When the patient has achieved a reasonable clinical result (usually a 75% decrease in psoriasis from baseline), the dosage may be decreased by 0.5 mg/kg per month. Neoral may be used continually for up to 2 years, as long as the patient is properly monitored and does not have significant adverse events. Safety data beyond 2 years have not yet been established; therefore, it is at the discretion of the physician and the patient whether to continue treatment with Neoral beyond 2 years.

With respect to intermittent short-course therapy, the initial dose is the same as the continuous dose, but Neoral is discontinued after remission is achieved.[10] If the patient relapses, the drug may be reintroduced at the previously effective dose. Rotational therapy is always an option, but presently there are no guidelines. Other treatment options include the use of methotrexate, phototherapy, and acitretin. Combination therapy has been used in some cases; for example, cyclosporine and acitretin have been used to treat erythrodermic psoriasis.[11] The use of methotrexate and cyclosporine has been well studied in the treatment of rheumatoid arthritis[12]; a recently published report using a combination for psoriasis treatment indicated good control using lower doses of both drugs.[13] I have experienced similar results with this dosing.

Adverse Events

The 2 most important adverse events are renal dysfunction and hypertension, which usually develop within the first 3 months of the introduction of cyclosporine. With early detection and proper dosage adjustments, or with the discontinuation of cyclosporine, these adverse events are usually reversible. Renal dysfunction seems to be dose related and is more likely to present in patients whose dosages are greater than 5.0 mg/kg per day. If hypertension is not adequately controlled by dosage adjustment, it can be treated with nifedipine, a calcium channel blocker. Nephrotoxicity can be induced with the concomitant use of medications that are potentially nephrotoxic (Table I). The use of multiple drugs, especially cotrimoxazole, trimethoprim, and ciprofloxacin, may result in nephrotoxicity, and cyclosporine nephrotoxicity is more likely to be permanent if the serum creatinine level rises and is maintained above 30% of baseline.[14] Although nonsteroidal anti-inflammatory drugs (NSAIDs) are suspected of having potential interactions that result in added nephrotoxicity, significantly elevated creatinine levels have been observed in multiple patients who have taken cyclosporine and NSAIDs.

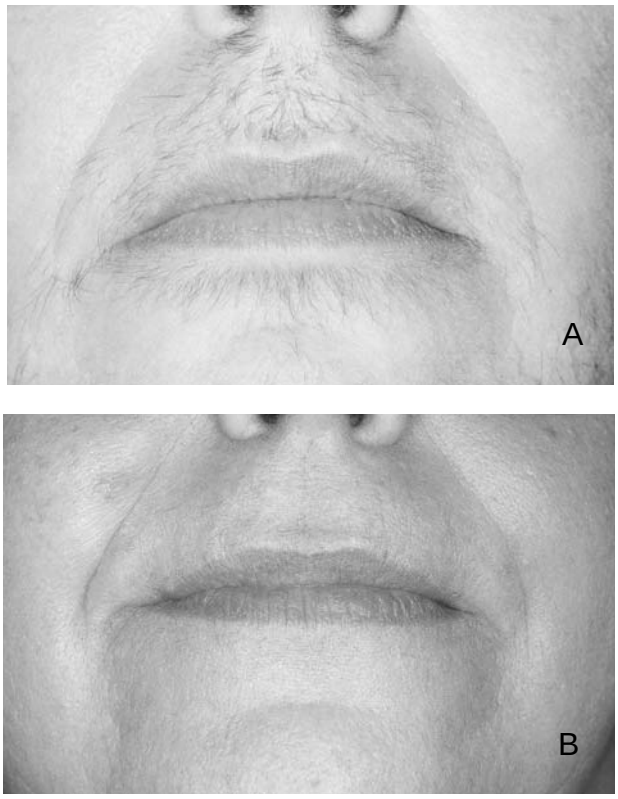

FIGURE 2. Cyclosporine-induced hypertrichosis before (A) and after (B) laser treatment.

If creatinine levels rise above 30% of baseline, potentially nephrotoxic medications should be discontinued, and the creatinine level should be retested within 2 weeks. If the creatinine level does not return to normal, the dosage of Neoral should be decreased by 1.0 mg/kg per day and the creatinine level should be retested in 1 month. If creatinine levels return to normal, this dosage may be maintained; however, if creatinine levels do not return to within 30% of baseline, Neoral should be discontinued. If the creatinine level doubles, Neoral should be discontinued and the creatinine checked after 1 month.[6]

Another important side effect is cutaneous malignancy: psoriasis patients have a 7.5-fold increased risk of developing skin cancers.[14] At present, there is debate over whether this is associated with cyclosporine or other therapy received by the patient, such as psoralen ultraviolet light therapy. Other potential side effects include paresthesia, gastrointestinal upset, abdominal pain, headache, hypertrichosis, and gingival hyperplasia. These adverse events are usually mild and transient and resolve spontaneously or upon discontinuation of the

Table I.

Summary of Drug Interactions*

	Drugs Increasing the Serum Concentration of Cyclosporine	Drugs Decreasing the Serum Concentration of Cyclosporine	Drugs Causing Additive Nephrotoxicity
Substantiated Interactions	Calcium channel blockers: • Diltiazem • Nicardipine • Verapamil Corticosteroids Doxycycline Erythromycin Imipenem Josamycin Ketoconazole Methylprednisolone Metoclopramide Norethisterone or danazol Oral contraceptives Propafenone	Barbiturates Carbamazepine Methimazole Nafcillin Octreotide Phenytoin or phenobarbital Rifampin IV Sulfadimidine IV Trimethoprim IV	Aminoglycerides Amphotericin B Ciprofloxacin Colchicine Cotrimoxazole or trimethoprim Melphalan
Suspected or Potential Interactions	Acyclovir Androgenic steroids Cephalosporins Furosemide H_2 antagonists Thiazide diuretics Warfarin	Anticonvulsants Sulfinpyrazone	NSAIDs
	Alteration of Immunosuppressive Effects	**Interactions With Alcohol Content**	**Other**
Miscellaneous Interactions	Etoposide Propranolol Verapamil	Chlorpropamide Disulfiram Metronidazole	Captopril Colchicine Digoxin HMG-CoA reductase inhibitors Nifedipine† Prednisolone Toxoids or vaccines

*Per product monogram (Canada).
†Should be avoided in patients who develop gingival hypertrophy.

medication. Women who develop hypertrichosis may benefit from laser treatment (Figure 2, A and B). Multiple laboratory abnormalities, such as hypomagnesemia, hyperkalemia, elevated lipids, glucose, and uric acid, also have been observed, but are not usually significant and do not require discontinuation of therapy.

Discussion

The addition of cyclosporine to the treatment regimen for severe psoriasis has given patients a safe and effective therapy that has predictable and, for the most part, treatable adverse events, most of which completely resolve with discontinuation of therapy. The therapeu-

tic regimen chosen will depend on a patient's response to cyclosporine. Although rotational or intermittent therapy is most desirable, some patients will require continuous therapy. The use of combination therapy with psoralen ultraviolet light therapy is not recommended; however, patients who fail cyclosporine in our clinic are sometimes be treated with a combination of cyclosporine and methotrexate, which is beneficial in some patients with rheumatoid arthritis. Other combination therapies that have been used include cyclosporine with acitretin.

The use of cyclosporine has enabled physicians to offer therapy to patients who suffer from severe psoriasis, thus enabling them to gain greater control over their disease. The need for careful evaluation before therapy and the necessity for strict monitoring of the patient cannot be overemphasized because untreated hypertension and renal dysfunction may lead to serious, nonreversible morbidity. Physicians who wish to use Neoral should review the published guidelines, make themselves aware of drug interactions, and be very cautious with the use of NSAIDs and other potentially nephrotoxic drugs. If the guidelines are followed, most patients will control their psoriasis with a low risk of drug toxicity.

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