Report

# Safety issues with cyclosporine

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The more even absorption characteristics of the Neoral® formulation of cyclosporine contribute to its improved safety profile when compared with Sandimmune®. Excessive dose adjustments of cyclosporine are reduced, stable absorption is offered, and variability in cyclosporine blood levels is avoided. Short-term use of Neoral, i.e. for treatment up to 1 year, also enhances its overall safety.

As discussed in other articles in this supplement, the potential for side-effects of Neoral may be reduced by careful patient selection and by proper dosing. The adverse effects that may be associated with appropriate dosing of Neoral are reviewed in this article.

## Early vs persistent symptomatic adverse events

The symptomatic adverse reactions that occur with cyclosporine therapy fall into two types. First are those reactions that occur in a concentration-dependent fashion during initial therapy, including gastrointestinal distress, fatigue, headache, malaise, and joint or muscle discomfort. These reactions typically resolve without treatment after several weeks. Tremors and paresthesias have been reported, although they occur infrequently at doses of cyclosporine recommended for dermatologic conditions. When present, the symptoms are likely to improve with time during therapy.

Second are the more persistent, clinically evident reactions that include hypertension, hirsutism, and gingival hyperplasia.

The overall risk of developing hypertension while on cyclosporine therapy is variable. As would be expected, the risk is greater in older patients and in those who have higher baseline blood pressures. Persistent hypertension, i.e. blood pressure greater than 140/90 mm Hg, can often be managed with salt restriction, exercise, and fish oil; antihypertensive drug therapy is used when other measures fail.

The incidence of drug-induced hirsutism is ≈25% within the first 4 months of treatment.[1] The problem appears to involve primarily terminal hair. Gingival hyperplasia occurs in ≈10%–15% of patients[1] and can be ameliorated at least in part by careful dental hygiene.

Table 1 lists the reasons why patients in clinical trials at our center discontinued therapy over an extended treatment period of 3 years. Eighty-five patients began the study. After ≈1, 2, and 3 years, 64, 27, and 16 patients, respectively, remained in the protocol. Currently, treatment periods of 1 year or less are recommended.

## Serious adverse effects

### Laboratory values

The most common changes in laboratory test values associated with Neoral are shown in Table 2. Increases in uric acid or bilirubin are not generally of concern in patients who are receiving the doses of Neoral appropriate to dermatologic conditions. Hyperlipidemia induced by cyclosporine is usually mild and often can be managed by dietary changes, by increased physical activity, or, when necessary, by pharmacologic intervention. Replacement magnesium therapy may be necessary in some patients.

### Renal toxicity

The primary concern with the recommended use of Neoral is the potential for toxic effects on the kidney.[2–4] The early and reversible vasoconstrictive activity of the drug may precipitate a rise in serum creatinine concentrations within the first few weeks of therapy.[1] After at least 1 year of treatment, cyclosporine therapy

**Table 1** Reasons for stopping cyclosporine therapy during 3-year, single-center clinical trial*

| Category† | Percentage of patients who left study ($N = 69$) |
|---|---|
| Patient violated protocol, moved away, or miscellaneous reasons | 33 |
| Kidney-related side-effects‡ | 33 |
| Unrelated illnesses | 14 |
| Cardiovascular side-effects§ | 10 |
| Lack of efficacy of cyclosporine | 4 |
| Entered long-term remission during cyclosporine therapy | 4 |
| Total | 98¶ |

*The current recommendation is to treat for periods of 1 year or less.
†The author has combined various reasons for leaving the study into these categories.
‡Includes elevations in serum creatinine or urea nitrogen, decline in glomerular filtration rate, renal biopsy evidence of fibrosis, and patients in whom concern was raised about their requirement for concurrent use of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs.
§Includes hypertention, migraines, and other heart or vascular conditions.
¶Does not total 100 because of rounding.

**Table 2** Laboratory changes associated with Neoral therapy

| Increased values | Decreased values |
|---|---|
| Creatinine | Glomerular filtration rate |
| Urea nitrogen (BUN) | Magnesium |
| Cholesterol/triglycerides | |
| Bilirubin | |
| Uric acid | |

is also associated with tubular atrophy and interstitial fibrosis.[5–7] None of the patients in our clinical trials, including those receiving treatment for as long as 3 years, required treatment for kidney disorders. The long-term potential for progressive renal failure requires further clarification, however, as does the impact of other variables, such as ageing or the use of such agents as nonsteroidal anti-inflammatory drugs on declining renal function.

What are the clinical implications with regard to renal toxicity? In general, the potential for toxicity can be minimized by doses that do not exceed 5 mg/kg per day of either Neoral or Sandimmune, and by dosage reduction in the event that serum creatinine rises more than 30% above baseline values. Fish oil supplements have been suggested to minimize renal toxicity.[8,9] Measurement of glomerular filtration rate may be useful in monitoring renal function in patients with pre-existing risk factors for kidney disease or in patients receiving cyclosporine beyond the recommended time course. The use of short-term therapy would also be expected to avoid the occurrence of irreversible renal dysfunction.

### Cancer

The development of cancer as a result of cyclosporine therapy is an extremely rare phenomenon,[10] particularly when compared with the more straightforward relationship between the drug and renal side-effects. The occurrence of lymphoma or other cancers more likely reflects the degree of deep immunosuppression induced by this class of agents, but this is not as great a concern with the treatment of psoriasis, where cyclosporine is administered in doses below 5 mg/kg per day for intermittent periods, and without other immunosuppressive agents.

### Cutaneous side-effects

Infections such as warts, impetigo, and tinea are of concern in transplant patients receiving cyclosporine; however, this is not a substantive problem in patients receiving low doses for treatment of psoriasis.[1]

Rare side-effects of Neoral include isolated case reports of severe acne, folliculitis, and reversible benign lymphocytic infiltrates.[10,11]

## Monitoring guidelines

Table 3 contains monitoring recommendations prior to and during Neoral therapy. An accurate baseline serum creatinine measurement is important in order to assess

**Table 3** Recommendations for monitoring prior to and during Neoral therapy

| Parameter | Action |
|---|---|
| **Prior to therapy** | |
| Serum creatinine | Obtain at least two measurements within 10% of each other to determine true baseline level |
| **At baseline, after 2 and 4 weeks, and then at least monthly** | |
| Blood pressure | Treat hypertension or reduce cyclosporine dose if possible |
| Creatinine | Reduce cyclosporine dose if value > 30% over baseline |
| Urea nitrogen | Assess kidney function further if significantly and persistently abnormal |
| Lipids | Treat if significantly abnormal |
| Bilirubin, liver function | Expect increases, but dose reduction usually not indicated in bilirubin |
| Uric acid | Treat if significantly abnormal |
| Magnesium | Provide replacement therapy if low |
| Electrolytes | Treat if significantly abnormal |
| New medications | Determine if new medication affects or is affected by cyclosporine metabolism |

Adapted from Ellis CN, Cyclosporine in the treatment of severe psoriasis. In: Weinstein GD and Gottleib AB (eds). *Therapy of Moderate-to-Severe Psoriasis*. Portland, Ore: The National Psoriasis Foundation, 1993: 115.

changes during therapy, and two separate baseline tests within 10% of each other help overcome procedural inaccuracies.

Out-patient urine creatinine clearance tests tend to be unreliable. Creatinine clearance can be calculated from formulas based on serum creatinine but, for many patients, adds little practical information. Glomerular filtration rates are probably unnecessary in most patients when cyclosporine is used for the treatment of psoriasis as recommended.

Blood pressure should be followed every 2 weeks for the first 4 weeks' of therapy, and monthly thereafter. It is not usually necessary to track blood levels of cyclosporine routinely, but measurement may be helpful in the rare patient who does not experience any clinical improvement on therapy. In this case, the cyclosporine blood level may differentiate a true nonresponder from a patient experiencing poor absorption. Because many laboratories use transplantation indications as their reference for normal levels of cyclosporine, the reported laboratory "normal range" may not be helpful.

## The future literature on Neoral

Now that Neoral is approved by the Food and Drug Administration for use in psoriasis, it is likely that there will be a substantial increase in usage. This will likely lead to a number of reports of side-effects published by dermatologists in the dermatologic literature. Readers of these reports should recognize that many of the side-effects will occur once or rarely. Further, readers should not expect to see a balancing number of articles on the efficacy of cyclosporine because the results of cyclosporine therapy in many of the responsive disorders have already been published.

## Conclusions

The major organ at risk during cyclosporine therapy is the kidney; however, risk to renal function can be reduced by attention to dosing and routine measures of kidney function, specifically serum creatinine. When used within the guidelines and for periods of 1 year or less, cyclosporine, particularly the Neoral formulation, may provide substantial benefit to patients with psoriasis and other dermatologic conditions. Neoral is a formulation of cyclosporine that provides consistent and predictable absorption.

## References

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