RHEUMATOID arthritis (RA) is a painful and disabling condition that is increasingly widely recognized as being associated with early mortality. Since the late 1970s, clinical trials have been conducted in both Europe and North America to determine whether oral cyclosporin A (CyA) has a role in the management of RA, and, if so, how it might best be used.

That experience, plus advances in our understanding of the mechanisms of action of CyA and the pathology of RA, provided the foundation for the recommendations of the 1992 International Consensus Report on the use of CyA in RA [1]. These recommendations were updated at a subsequent International Review in 1994 [2]. The advice presented below is derived from a further review of the recommendations, in which a trend towards early implementation of therapy, increased clinical experience with CyA, and the development of the new microemulsion formulation of CyA (Sandimmun Neoral®) were taken into consideration.

A secondary goal of the review was to provide clear and accessible guidance to physicians wishing to prescribe the CyA microemulsion to their patients with RA, within the context of specific national prescribing information. The assumption is made that CyA will be administered outside experimental research protocols by physicians experienced in the management of RA.

WHOM DO WE TREAT AND WHEN?

Clinical trials show CyA to be effective in patients with active RA. CyA may be considered for the treatment of patients who are candidates for second-line therapy, and should be selected on the same basis as other second-line agents. Furthermore, CyA may be used in patients with early persistent RA, and advanced RA, for whom CyA is considered to be the most appropriate available option in the view of both physician and patient. These recommendations are supported by the following considerations:

(i) the prognosis of RA remains poor, despite the earlier use of traditional disease-modifying antirheumatic drugs for most patients;
(ii) clinical and radiographic evidence of disease progression can be used to identify more readily some patients who are likely to become severely affected by RA at an early stage of their disease;
(iii) risk factors for CyA toxicity are now established and patients can be monitored appropriately.

WHOM SHOULD WE NOT TREAT?

The following recommendations include contraindications for the use of CyA and situations in which caution is advised. However, it may on rare occasions be desirable to administer CyA, or indeed any medication, in the presence of a contraindication. A physician contemplating such a measure is advised to seek advice from colleagues and relevant specialists to make a fully informed risk/benefit assessment.

Contraindications
(i) Current or past malignancy (except basal-cell carcinoma). [Very remote malignancy may be cause for caution rather than a contraindication. However, malignancy of the haematopoietic system, including the lymph nodes, and skin malignancy (with the exception of basal-cell carcinoma) are strong contraindications, however remote.]
(ii) Uncontrolled hypertension.
(iii) Renal dysfunction (abnormal serum creatinine).
(iv) Liver function tests more than twice the upper limit of normal.

Caution in use
The following factors increase the risk of adverse effects from CyA. If one of these factors is present, the potential risks of therapy should be weighed carefully against the benefits.

(i) Age more than 65 yr.
(ii) Controlled hypertension.
(iii) Immunodeficiency (except selective IgA deficiency).
(iv) Abnormally low white blood cell count (unless due to Felty’s syndrome).
(v) Obesity.
(vi) Use of drugs that interfere with the bioavailability or metabolism of cyclosporin (see Table I), or are known to have nephrotoxic potential (e.g. aminoglycosides, amphotericin B).
(vii) Concurrent or previous use of alkylating agents such as cyclophosphamide.
(viii) Premalignant conditions such as leucoplakia, monoclonal paraproteinaemia, myelodysplastic syndrome and dysplastic naevi.
**TABLE I**

<table>
<thead>
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<th>Drugs interfering with cyclosporin A metabolism</th>
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<td>Increasing concentration</td>
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<td>Ketoconazole and otherazole derivatives</td>
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<td>Macrolide antibiotics (including erythromycin, josamycin)</td>
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<tr>
<td>Calcium channel blocking agents (such as diltiazem, nicardipine, verapamil, but not nifedipine, isradipine, niliedipine*)</td>
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*As nifedipine may cause gingival hyperplasia, it is advised that it should be avoided in patients who develop gingival hyperplasia with CyA therapy.

(i) Active infection may necessitate temporary discontinuation.

(x) Pregnancy and lactation. [Experience with CyA in pregnant women remains limited. Data available from organ-transplant recipients indicate that, compared with traditional therapy, CyA imposes no increased risk of adverse effects on the course and outcome of pregnancy. However, as there are no adequate and well-controlled studies in pregnant women, CyA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. CyA passes into breast milk. Mothers receiving treatment with CyA should not breast feed.]

**RECOMMENDATIONS PRIOR TO THERAPY**

Before CyA therapy is started, the patient’s complete medical history and current characteristics should be documented, and patients with potential risk factors for renal dysfunction should be excluded. Metlicus verbal instructions (and written instructions, if available) concerning the risks, benefits, nature and implementation of CyA treatment should be given to the patient. Physical and laboratory examinations should be conducted, including assessment of the following.

(i) Blood pressure.

(ii) Serum creatinine on at least two separate occasions to ensure accurate baseline values [if the serum creatinine findings consistently suggest renal dysfunction, it is recommended that the glomerular filtration rate (GFR) be assessed directly or indirectly before initiating treatment].

(iii) Bilirubin.

(iv) Liver enzymes.

(v) Serum potassium.

(vi) Urinary protein.

**RECOMMENDED DOSING GUIDELINES TO OPTIMIZE TREATMENT**

**Initial treatment**

The starting dose of the CyA microemulsion should be 2.5–3.0 mg/kg per day. The drug is recommended to be administered in a twice-daily oral regimen, although a single daily dose may be acceptable.

**Continuing treatment**

The overall aim of treatment with CyA is to titrate the dose according to efficacy and tolerability to achieve the optimum balance between benefit and risk.

If there is a clinical response after 4–8 weeks, and optimal efficacy is considered to have been achieved, continue at the same CyA dose.

If there is no clinical response or only a partial clinical response after 4–8 weeks, the CyA dose should be titrated upwards. Incremental increases of 0.5 to maximally 1.0 mg/kg are recommended at 1- to 2-month intervals, to a maximum dose of 5 mg/kg per day. Particular caution should be exercised with doses of >4.0 mg/kg per day.

If an effective maximum tolerable dose of CyA is being administered, and no further improvement is expected, and the patient has been stable for at least 3 months, the dose should be decreased monthly or every 2 months in increments of 0.5 mg/kg to the lowest effective dose. An effective dose is one agreed to be so by a consensus of the patient and physician.

If CyA is only partially effective after 3 months at the maximum tolerable dose, another medication should be considered to be used concomitantly or to replace CyA.

If there is essentially no clinical response by 6 months, and the maximum tolerable dose has been administered for at least 3 months, CyA should be discontinued.

The recommended dosing guidelines for the CyA microemulsion are summarized in the algorithm in Fig. 1.

**RECOMMENDED MONITORING GUIDELINES TO OPTIMIZE TREATMENT**

These monitoring guidelines were originally developed at an earlier consensus conference on CyA for psoriasis [3] and were agreed at the previous International RA Consensus Meetings to be appropriate for patients with RA during the first 3 yr of therapy.

![Fig. 1.—Recommended dosing guidelines to optimize treatment.](image)
**CONVERSION FROM THE ORIGINAL CYCLOSPORIN A FORMULATION TO THE MICROEMULSION FORMULATION**

When converting patients from the original CyA formulation to the microemulsion formulation, a 1:1 dose-conversion strategy is recommended. The rationale for such an approach is that, in patients who are good absorbers of CyA from the original formulation, the absorption of CyA is unlikely to change post-conversion. However, in patients who were poor absorbers of CyA from the original formulation, the absorption of CyA appears to increase post-conversion. As a result, it may be necessary to make subsequent dose reductions in these patients, to ensure that they are receiving the lowest effective dose. All dose adjustments post-conversion should be conducted according to the recommended dosing guidelines for safety and efficacy, and doses should not exceed 5 mg/kg body weight per day, with caution exercised with doses >4 mg/kg per day.

Careful safety monitoring is mandatory post-conversion.

Blood pressure and serum creatinine should be measured prior to conversion and 1, 3 and 7 weeks thereafter. If the patient exhibits abnormal blood pressure or serum creatinine values prior to conversion, caution should be exercised. If the post-conversion blood pressure markedly exceeds the pre-conversion value, a reduction in CyA dose should be considered. If the post-conversion serum creatinine rises to >29% above the patient’s pre-treatment baseline value, the algorithm in Fig. 1 should be followed.

**COMBINATION THERAPY**

Evidence from at least two controlled, randomized clinical trials indicates that CyA in combination with other second-line agents produces clinically important benefit in the treatment of RA [4, 5]. On this basis, CyA could reasonably be considered for use in combination with second-line agents in patients who have exhibited suboptimal response to CyA alone.

This Consensus Conference took place in Rome, Italy, on 19 June 1996, under the sponsorship of Sandoz Pharma Ltd (Basel, Switzerland). The co-chairmen were Professor G. S. Panayi, Rheumatology Unit, United Medical and Dental Schools of Guy’s and St Thomas’ Hospital, London, and Professor P. Tugwell, Department of Medicine, University of Ottawa, Ottawa General Hospital, Ontario, Canada. The other participants were: B. A. C. Dijkmans, Department of Rheumatology, Free University Hospital, Amsterdam, The Netherlands; P. Emery, Rheumatology and Rehabilitation Research Unit, University of Leeds, Leeds; F. Fantini, Gaetano Pini Orthopaedic Institute, University of Milan, Milan, Italy; G. Ferraccioli, Rheumatic Disease Unit, University of Udine School of Medicine, Udine, Italy; R.-M. Flipo, Department of Rheumatology, R. Salengro’s Hospital, Lille, France; O. Forre, The National Hospital, Rheumatic Disease Center, Oslo University, Oslo, Norway; B. Manger, Medical Clinic III and Institute for Clinical Immunology, University of Erlangen, Erlangen, Germany; T. Pincus, Vanderbilt University, Department of Medicine, Division of Rheumatology, Nashville, TN, USA; A.-G. Schmidt, Clinical Research

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