Assessment of efficacy and acceptability of low dose cyclosporin in patients with rheumatoid arthritis

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SUMMARY The efficacy of cyclosporin in a double blind, placebo controlled trial of four months duration has previously been reported by us. To assess the benefit-to-risk ratio of cyclosporin this study was followed by a one year open trial including 49 of the previous 52 patients. Cyclosporin was given at an initial dosage of 5 mg/kg/day and then modulated on the basis of efficacy and renal toxicity. During the study the drug had to be discontinued in 32 patients: because of inefficacy in 10, side effects in 11, both in nine, and in two because of unrelated events. The significant clinical improvement noted at four months persisted through one year in the 17 patients who continued to receive treatment. Nephrotoxicity of the drug (24 patients) required constant and close monitoring as well as modulation of daily drug dosage during the trial. This study indicated that cyclosporin might be valuable in the treatment of patients with advanced rheumatoid arthritis, in whom other second line agents have failed.

The presumed mechanism of action of cyclosporin suggested clinical evaluation of its therapeutic potential in rheumatoid arthritis. Cyclosporin appears to block intercellular messages between inflammatory cells, probably by reducing production of interleukin 2 and other lymphokines.¹ Open trials have already suggested its dose dependent effectiveness in refractory rheumatoid arthritis but have also shown dose dependent toxicity.²⁻¹⁰ Moreover, these studies have provided investigators with a better knowledge of cyclosporin dosage and monitoring.

Two short term (four months) controlled studies confirmed this efficacy.^{11, 12} Serious concerns about long term side effects, however, especially renal toxicity, prompted us to pursue our controlled study¹¹ in a one year open study.

Patients and methods

PATIENTS

Forty nine outpatients of both sexes fulfilling the American Rheumatism Association criteria for definite or classical rheumatoid arthritis¹³ were recruited for the study after their written consent

had been obtained. Another criterion for entry was the presence of active disease, defined by at least three of the following: erythrocyte sedimentation rate 30 mm/h or higher, 60 minutes or more of morning stiffness, Ritchie articular index¹⁴ of 10 or more, Lee functional index¹⁵ of 5 or more, and at least three joints with effusion or synovitis. Excluded from the study were patients with a serious concomitant medical illness, with vasculitis, judged to be in functional class IV (American Rheumatism Association criteria¹⁶), with a history of liver disease (defined by a rise of liver enzymes to a level twice above baseline or by a bilirubin concentration above baseline), or renal disease (defined by a creatinine concentration greater than 120 $\mu\text{mol/l}$) and patients having high blood pressure, even if well controlled by drugs. Before entering the trial the patients underwent a wash out period of three months without any disease modifying drugs. Prednisone under 15 mg/day, non-steroidal anti-inflammatory drugs, and analgesics were permitted if the dosage had been stable for one month.

STUDY DESIGN

The first part of the study (a double blind, placebo controlled trial of four months' duration with two parallel groups of 26 patients) has already been reported.¹¹ After the fourth month we broke the

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randomisation code and proposed treatment with cyclosporin to the patients who had received and failed with placebo treatment during the first part of the study (23 accepted) and to the 26 patients who had initially received cyclosporin and considered this treatment to be good or very good. We report here the results of a one year treatment period in these 49 patients.

DRUG ADMINISTRATION

Cyclosporin was supplied in liquid solution for oral administration and was given twice daily. The initial dosage was 5 mg/kg/day in all patients, except those concurrently taking cimetidine (seven cases), in whom the initial dosage was 2.5 mg/kg/day. This was reduced by half if renal toxicity occurred (defined as an increase of more than 50% in plasma creatinine concentration over baseline or plasma creatinine concentration >150 µmol/l, or both). In such cases creatinine was reassessed one week after dosage reduction and cyclosporin was again reduced by half if renal toxicity persisted. If the creatinine concentration was not acceptable one week after the second reduction, cyclosporin was discontinued. Hypertension (defined as observation at two consecutive consultations of diastolic pressure >95 mmHg and systolic pressure >150 mmHg in 18 to 50 year old patients and by diastolic pressure >100 mmHg and systolic pressure >160 mmHg in 50 to 75 year old patients) was treated according to standard practice. If hypertensive treatment was ineffective within two weeks the cyclosporin dosage was reduced by half and discontinued if hypertension persisted one more week despite dosage reduction.

After one month of treatment the cyclosporin dosage was increased by 1 mg/kg/day if clinical efficacy had not been achieved.

CLINICAL EFFICACY CRITERIA

Overall patient assessment was chosen as the primary criterion. Efficacy was evaluated on a five point scale (very good, good, moderate, poor, and very poor). After the fourth months' evaluation cyclosporin was continued only in patients considering this treatment as good or very good.

In addition, we evaluated the number of patients satisfying the American Rheumatism Association criteria for clinical remission.¹⁷

Other criteria used to assess disease activity were pain evaluated on a visual analogue scale of 100 mm, duration of morning stiffness, number of swollen joints, Ritchie articular index,¹⁴ and daily corticosteroid intake.

Patients were followed up on an outpatient basis, twice during the first month, monthly for six months, and at three month intervals thereafter.

CLINICAL MONITORING

Blood pressure, heart rate, weight, and spontaneous patient complaints were recorded twice during the first month and then monthly.

LABORATORY ASSESSMENT

Laboratory assessment was made at the beginning of cyclosporin treatment and at each examination. It included complete blood count and differential platelet count, Westergren sedimentation rate, plasma creatinine concentration, electrolytes, serum magnesium concentration, plasma uric acid concentration and liver enzymes. Determination of rheumatoid factor titres by the Waaler-Rose test was carried out at entry and after two and four months. The presence of protein and blood in the urine was also assessed at each visit.

STATISTICAL ANALYSIS

Qualitative variables were compared by the χ^2 test, quantitative variables by the non-parametric Mann-Whitney U test for intergroup comparisons and by the non-parametric Wilcoxon test for intragroup comparisons. The threshold of significance adopted was 5% (two tailed). The treatment termination incidence curves were evaluated by the Kaplan-Meier method.

Results

PATIENTS AND STUDY COURSE

Table 1 summarises the basic characteristics of the 49 patients. Seven patients withdrew from the study within the first four months owing to side effects. After the four month evaluation 15 other patients discontinued cyclosporin: seven for inefficacy, seven for inefficacy and side effects, and one for an unrelated event. Between the fourth and 12th month 10 more patients discontinued the drug: three for inefficacy, four for side effects, two for inefficacy and side effects, and one for an unrelated event.

Table 1 Demographic data of the 49 patients included in the study

Age (years)*	55.0 (11.9)
Sex (female/male)	45/4
Duration of disease (years)*	13.6 (9.9)
Prior second line agents (number of patients)	
Hydroxychloroquine	38
Gold salts	46
D-Penicillamine	40
Immunosuppressive drugs	8
Positive rheumatoid factor	39
HLA-DR4 positive	23
Prednisone consumption* (mg/day)	7.5 (4.7)

*Values are given as mean (SD).

Table 2 Clinical and biological variables in patients at the start of cyclosporin treatment, after four months, and after one year. Values are given as mean (SD)

Variables	Start of cyclosporin treatment (n=49)	After four months' treatment (n=42)	After one year's treatment (n=17)
Pain (100 mm visual analogue scale)	61.0 (25.0)	46.5 (25.6)*	42.2 (29.6)*
Ritchie articular index	17.9 (8.6)	12.2 (8.3)*	5.9 (6.4)*
Morning stiffness (min)	147.4 (132.6)	68.8 (108.8)*	53.0 (100.8)*
Number of swollen joints	14.0 (8.5)	8.4 (7.2)*	5.8 (4.5)*
Erythrocyte sedimentation rate (mm/1st h)	49.6 (27.3)	46.0 (25.1)	63.2 (33.8)
Platelets ($\times 10^9/l$)	433 (152)	380 (150)*	335 (104)*

* $p < 0.0001$ determined by the non-parametric Wilcoxon test comparing values obtained during the study with baseline values.

The mean (SD) cyclosporin daily dosage was 4.6 (0.9) mg/kg/day at entry (49 patients), 4.8 (1.7) mg/kg/day at the fourth month (42 patients), and 3.8 (1.5) mg/kg/day after one year (17 patients).

EFFICACY ASSESSMENT

After four months of treatment 27 patients (out of the 49 enrolled and out of the 42 who completed the four months of the trial) considered the efficacy of treatment as good or very good. At this time all clinical variables were improved (Table 2) when compared with baseline, and morning stiffness had completely disappeared in 17 out of the 42 patients. None fulfilled the American Rheumatism Association criteria for clinical remission, however.

The clinical improvement noted at four months persisted for one year in the 17 patients who continued to receive treatment (Table 2). Moreover, in these patients there was a significant reduction in mean (SD) corticosteroid consumption (6.3 (4.2) mg/day at the beginning, 5.6 (3.6) mg/day after four months of cyclosporin treatment, and 4.4 (2.8) mg/day after one year; $p = 0.005$).

Of the 11 patients who discontinued cyclosporin because of side effects, and in whom cyclosporin had been effective, recurrence of the disease was observed in eight after one to five weeks (mean: four weeks). Despite clinical improvement there was no significant change in rheumatoid factor titre. At entry 29 of the 42 patients who completed four months of treatment had a titre $>1/16$; 11 of these patients had a decrease in titre by at least two dilutions at four months, whereas four of the 13 patients who had a rheumatoid factor titre $<1/16$ at entry experienced an increase in this variable by at least two dilutions.

TOXICITY ASSESSMENT

Table 3 summarises the side effects which occurred during the study as well as those which prompted discontinuation of cyclosporin. Figure 1 shows that although side effects occurred more often during the

Table 3 Adverse reactions and causes of withdrawal of the 49 patients with rheumatoid arthritis treated with cyclosporin. Figures show number of patients

Side effects	Frequency	Cause of withdrawal*
Hypertrichosis	25	3
Renal toxicity	24	2†
Paraesthesia	17	3
Nausea	15	2
Hypertension	11	5
Epigastric discomfort	9	0
Gingivitis	9	0
Fatigue	6	0
Tremor	3	1
Benign gynaecomastia	2	0
Nervousness	1	0
Headache	1	0
Skin rash	1	0
Herpes zoster infection	1	0

*Five patients complained of at least two side effects at the time of cyclosporin discontinuation.

†Only two patients withdrew from the study because of renal toxicity, but in nine others disease activity recurred after cyclosporin daily dosage reduction, and cyclosporin treatment was then discontinued.

first six months, renal toxicity was observed at eight months in two patients, and high blood pressure the eighth and 11th month in two other patients.

Among the side effects observed, renal toxicity, haematological toxicity, hypertension, and paraesthesia merit more details.

Renal toxicity

A rise in plasma creatinine concentration of 50% over baseline or greater than 150 $\mu\text{mol/l}$ was observed in 24 of the 49 patients but prompted withdrawal of the drug in only two. Clinical characteristics of patients who developed renal toxicity were compared with those of patients who did not (Table 4). Renal toxicity was observed more frequently in patients over 60 years old or with plasma creatinine concentration $>90 \mu\text{mol/l}$ at entry.

Fig. 1 Date of onset of adverse reactions in the 49 patients with rheumatoid arthritis treated with cyclosporin.

Table 4 Predisposing factors of renal toxicity* in the 49 patients with rheumatoid arthritis treated with cyclosporin

Characteristics	Renal toxicity		p Value†
	Yes	No	
Number of patients	24	25	
Age (years)	59.1 (8.5)‡	51.7 (13.2)	<0.05
Patients >60 years	14	7	<0.05
Plasma creatinine concentration at entry (µmol/l)	90 (18)‡	71 (9)	<0.05
Plasma creatinine concentration at entry >88 µmol/l (patients)	7	1	<0.05
Concomitant use of cimetidine (patients)	5	2	NS
Concomitant NSAID§ intake (patients)	20	18	NS

*Defined as an increase in plasma creatinine concentration >50% over baseline or >150 µmol/l.
†Statistical analysis: χ^2 test for qualitative variables and Mann-Whitney bilateral U test for quantitative variables.
‡Values are mean (SD).
§NSAID=non-steroidal anti-inflammatory drug.

Plasma creatinine concentration changed from 80 (18) µmol/l (49 patients) before treatment to 106 (27) µmol/l (42 patients) after four months and to 97 (18) µmol/l (17 patients) after one year.

In the 32 patients who had to discontinue cyclosporin before the end of this one year study the plasma creatinine concentration rose from 80 (18) µmol/l before treatment to 106 (27) µmol/l at the end point of cyclosporin treatment and decreased to 88 (27) µmol/l one month after the discontinuation of the drug and to 80 (27) µmol/l after three months. Plasma creatinine concentration returned to the basal value in all patients except two. In one of them the diagnosis of renal amyloidosis was confirmed by renal biopsy eight months after cyclosporin discontinuation and in the other systemic vasculitis developed three months after cyclosporin withdrawal.

Non-steroidal anti-inflammatory drugs were withdrawn during the trial while cyclosporin dosage remain unchanged in six patients. Their mean plasma creatinine concentration was 80 (62–97) µmol/l at entry, 106 (88–124) µmol/l with concurrent non-steroidal anti-inflammatory drug treatment, and 97 (71–115) µmol/l without non-steroidal anti-inflammatory drugs. The difference is not statistically significant.

Haematological toxicity

Despite a significant improvement in the clinical condition of patients the haemoglobin concentration decreased from 117 (10) g/l to 113 (12) g/l after four months of treatment (42 patients, $p<0.005$). A loss of more than 10 g/l occurred in 15 patients and more than 20 g/l in three patients. Moreover, there was a slight but significant increase in the mean cell volume from 83.7 (6.8) to 84.8 (6.0) fl after four months of treatment ($p=0.04$) and in the total bilirubin concentration (from 5.5 (2.0) to 9.1 (3.5) µmol/l, $p<0.001$), while other liver enzymes did not increase. A significant correlation was observed between changes in haemoglobin concentration and (a) changes in mean cell volume ($r=0.562$, $p<0.0001$) and (b) changes in plasma bilirubin concentration ($r=0.325$, $p=0.033$) but not with the changes in plasma creatinine concentration ($r=-0.106$, $p=0.511$). Reticulocyte counts were available in only eight patients and were always lower than 80×10^9 cells/l. Haptoglobin values were obtained in 26 patients and showed a decrease from 4.9 (1.2) g/l at entry to 3.8 (1.2) g/l at four months. A similar decrease in α_1 -glycoprotein acid was observed; thus the haptoglobin/ α_1 -glycoprotein acid ratio remained unchanged (2.5 (0.5) v 2.4 (0.5)).

Paraesthesia

Seventeen of the 49 patients complained of paraesthesia, resulting in withdrawal of three patients. Onset of paraesthesia occurred during the first month in 11 patients and disappeared despite

Incidence treatment termination

Fig. 2 Treatment termination incidence curves in the 49 patients with rheumatoid arthritis treated with cyclosporin. — = treatment termination; □□□□ = inefficacy; ▲▲▲▲ = side effects.

cyclosporin continuation in eight (median duration: one month).

Patients who complained of paraesthesia tended to have lower pretreatment serum magnesium concentrations (0.78 (0.04) ν 0.81 (0.05) mmol/l, $p=0.057$). Serum magnesium concentration decreased from 0.80 (0.05) mmol/l before treatment to 0.71 (0.07) mmol/l at week 2 ($p<0.001$) in all 49 patients. At this time serum magnesium concentration was lower in patients who then had or subsequently developed paraesthesia (0.67 (0.03) ν 0.74 (0.08) mmol/l, $p<0.02$).

Hypertension

Despite medical treatment (nicardipine) hypertension resulted in withdrawal of five of the 11 patients in whom this side effect occurred. Moreover, two patients are still being treated 11 and 19 months after discontinuation of cyclosporin.

Some discrepancies were observed between the occurrence of hypertension and nephrotoxicity. Only seven patients developed both renal toxicity and hypertension after cyclosporin treatment. Thus renal toxicity did not occur in four of the 11 patients who developed hypertension, and hypertension did not occur in 17 of the 24 patients who showed renal toxicity.

LIFE TABLE ANALYSIS

Standard methods of life table analysis were applied to the 49 patients who entered the trial. Treatment termination was taken as the end point. Once generated, the total termination incidence curve was

partitioned according to the main reason for treatment termination: inefficacy or adverse effect. Figure 2 shows the incidence of treatment termination for all reasons, the termination incidence curve for treatment failure, and treatment termination due to adverse effects. By four months, 43% of patients taking cyclosporin had stopped treatment and by one year 65% of patients had stopped.

Discussion

This one year open study confirmed cyclosporin efficacy in refractory rheumatoid arthritis. Moreover, the number of patients included in the study and the duration of treatment allowed better analysis of the benefit-to-risk ratio.

BENEFIT

Although most of the 49 patients included in this study had previously received two or three remitting drugs, we observed an improvement in clinical status in 55% of them after four months of treatment. This improvement persisted up to one year in the 17 patients who tolerated the drug. Moreover, morning stiffness had completely disappeared in 17 out of the 42 patients after four months of treatment, and after both four months and one year there was statistical evidence for a steroid sparing effect of cyclosporin. No patient satisfied the American Rheumatism Association criteria for clinical remission of rheumatoid arthritis, however.¹⁷ The restrictive definition of nephro-

toxicity, which prompted us to reduce the cyclosporin daily dosage, reduced control of the disease, resulting in withdrawal of nine patients. This confirms the dose dependent efficacy of cyclosporin in rheumatoid arthritis² and suggests a narrow therapeutic window. The mean efficient daily dosage seems to be 4 mg/kg/day; the wide range observed in this variable, however, suggests that the useful daily dosage for an individual patient may vary from 2 to 7 mg/kg/day.

RISKS

We observed the common side effects previously reported.^{12 18-20}

Side effects were mostly observed during the first six months of treatment. The late occurrence of nephrotoxicity or hypertension, or both, in some patients, however, suggests that monthly clinical and biological monitoring is required indefinitely.

Renal toxicity of cyclosporin seems to be more frequent in patients with rheumatoid arthritis than in those with other autoimmune diseases.¹⁹⁻²¹ These discrepancies may be explained by (a) the age of the patients with rheumatoid arthritis. Our data showed a higher incidence of renal toxicity in patients over 60 years old. Moreover, rheumatoid arthritis usually occurs during the fifth decade, which is later than the onset of other autoimmune diseases; (b) a previous renal disease either associated with rheumatoid disease itself²² or due to long term concomitant non-steroidal anti-inflammatory drug treatment. We observed a higher incidence of nephrotoxicity in patients with a plasma creatinine concentration above 90 µmol/l before cyclosporin treatment, but no influence of concomitant non-steroidal anti-inflammatory drug treatment was shown. Despite this incidence of cyclosporin renal toxicity in patients with rheumatoid arthritis we never observed any irreversible deterioration of renal function in terms of plasma creatinine concentration. This might be explained by the close monitoring of the patients and the immediate modulation of the dosage in cases of renal toxicity.

Although we excluded patients with previous hypertension, this side effect was observed in 11 patients and warranted withdrawal of the drug in five of them. Our data showed a lower incidence of hypertension than that observed in Weinblatt's series (seven out of 10 patients studied), however,¹⁰ suggesting that previous hypertension still has to be considered a contraindication to the initiation of cyclosporin treatment. The necessity for this precaution is emphasised by the fact that two patients in our series still need medical treatment for hypertension despite cyclosporin discontinuation.

The mechanism of the decrease in haemoglobin

concentration observed in our series remains unclear. The statistically significant correlations between the changes in haemoglobin concentration and the changes in (a) the mean cell volume and (b) the total bilirubin concentration suggest haemolysis. No reticulocytosis and no elective or dramatic decrease in haptoglobin were observed, however.

Paraesthesia is a common feature in patients receiving cyclosporin.¹⁸⁻²⁰ Neurological side effects have been related to low serum magnesium concentration.²³ Our study suggests that (a) previous low serum magnesium concentration may be a predisposing factor for paraesthesia after cyclosporin treatment and (b) cyclosporin induces low serum magnesium concentrations in patients with rheumatoid arthritis. The relation between low serum magnesium concentrations and cyclosporin treatment and the efficacy of a preventive or curative therapy, or both, of this side effect with magnesium remains to be investigated.

Finally, the low percentage of patients still receiving treatment after one year (35% (17/49) in our series) suggests that the clinical benefit of cyclosporin may be poor. It should be borne in mind, however, that in our experience these data are very similar to those observed with other conventional slow acting drugs (32% of patients are still receiving treatment with gold salts after one year and 37% with D-penicillamine),²⁴ and that our study involved patients with advanced rheumatoid arthritis in whom other second line agents had failed. This indicates that cyclosporin, in association with close clinical and biological monitoring, may be valuable in the treatment of advanced refractory rheumatoid arthritis.

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References

- 1 Keown P A, Stiller C R. Mechanism of immunosuppression by cyclosporin. *Transplant Proc* 1981; **13**: 386-9.
- 2 Amor B, Dougados M. Cyclosporin in rheumatoid arthritis: open trials with different dosages. In: Schindler R, ed. *Cyclosporin in autoimmune diseases*. Berlin: Springer, 1985: 283-7.
- 3 Bombardier C, Tugwell P, Gent M, Buchanan W, Ludwind D, Stiller C. A pilot study of CyA in patients with rheumatoid arthritis. In: Schindler R, ed. *Cyclosporin in autoimmune diseases*. Berlin: Springer, 1985: 288.
- 4 Dougados M, Amor B. Cyclosporin A in rheumatoid arthritis: preliminary clinical results of an open trial. *Arthritis Rheum* 1987; **30**: 83-6.
- 5 Forre O, Bjerkhoel F, Salvensen C F, et al. An open controlled, randomized comparison of cyclosporin and azathioprine in the treatment of rheumatoid arthritis. A preliminary report. *Arthritis Rheum* 1987; **30**: 88-92.
- 6 Graf U, Marbet U, Muller W, Thiel G. Cyclosporin A: effects and side effects in the treatment of rheumatoid arthritis and psoriatic arthritis. *Immun Infekt* 1981; **9**: 20-8.

- 7 Hermann B, Muller W. Die therapie der chronischen polyarthritis mit Cyclosporin A, einem neuen immun-suppressivum. *Aktuelle Rheumatologie* 1979; **4**: 173-86.
- 8 Herzog Ch, Gross D. Low dose cyclosporin A and prednisone: a step in the direction of selective immunosuppression in rheumatoid arthritis refractory treatment (6-month follow-up). In: Schindler R, ed. *Cyclosporin in autoimmune diseases*. Berlin: Springer, 1985: 289-96.
- 9 Madhok R, Capell H A. Cyclosporin in rheumatoid arthritis: preliminary results. In: Schindler R, ed. *Cyclosporin in autoimmune diseases*. Berlin: Springer, 1985: 297-8.
- 10 Weinblatt M E, Coblyn J S, Fraser P A. Cyclosporin: a treatment of refractory rheumatoid arthritis. *Arthritis Rheum* 1987; **30**: 11-17.
- 11 Dougados M, Awada H, Amor B. Cyclosporin in rheumatoid arthritis: a double blind placebo controlled study in 52 patients. *Ann Rheum Dis* 1988; **47**: 127-33.
- 12 Van Rijthoven A W A M, Dijkmans B A C, Goei The H S. Cyclosporin treatment for rheumatoid arthritis: a placebo controlled, double blind, multicentre study. *Ann Rheum Dis* 1986; **45**: 726-31.
- 13 Ropes M W. Diagnostic criteria for rheumatoid arthritis, 1958 revision. *Ann Rheum Dis* 1959; **18**: 49-53.
- 14 Ritchie D M, Boyle J A, McInnes J M, Grieverson P, Buchanan W. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *J Med* 1968; **37**: 393-406.
- 15 Lee P, Jasani M K, Dick W C, Buchanan W. Evaluation of a functional index in rheumatoid arthritis. *Scand J Rheumatol* 1973; **2**: 71-7.
- 16 Steinbrocker O, Traeger C H, Batterman R C. Therapeutic criteria in rheumatoid arthritis. *JAMA* 1949; **140**: 659-62.
- 17 Pinals R S, Masi A T, Larsen R A, et al. Diagnostic and therapeutic criteria committee: preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981; **24**: 1308-15.
- 18 Nussenblatt R B, Palestine A, Chan C, Mochizutu M, Tancey P. Effectiveness of cyclosporin therapy for Behçet's disease. *Arthritis Rheum* 1985; **28**: 671-9.
- 19 Palestine A G, Nussenblatt R B, Chan C. Side effects of systemic cyclosporine in patients not undergoing transplantation. *Am J Med* 1984; **77**: 652-5.
- 20 Rudge P. The use of cyclosporin (CsA) in multiple sclerosis. Trial design and tolerance. In: *Cyclosporin in autoimmune disease, 1st International symposium, Basle*. 1985.
- 21 Stiller C R, Dupre J, Gent M, et al. Effects of cyclosporine immunosuppression in insulin-dependent diabetes mellitus after recent onset. *Science* 1984; **223**: 1362-7.
- 22 Breedveld F C, Valentijn R M, Westedt M L, Weening J. Rapidly progressive glomerulonephritis with glomerular crescent formation in rheumatoid arthritis. *Clin Rheumatol* 1985; **5**: 353-9.
- 23 Thompson C B, June C H, Sullivan K M, Thomas E J. Association between cyclosporin neurotoxicity and hypomagnesemia. *Lancet* 1984; **ii**: 1116-20.
- 24 Dougados M, Nguyen M, Duchesne L, Benjelloun M, Amor B. Appréciation de l'utilité des traitements de fond de la polyarthrite rhumatoïde par l'analyse du taux de maintenance thérapeutique. *Rev Rhum Mal Osteoartic* 1989; **56**: 89-92.