Cyclosporin in rheumatoid arthritis: a double blind, placebo controlled study in 52 patients

MAXIME DOUGADOS, HASSANE AWADA, AND BERNARD AMOR

From the Department of Rheumatology, Cochin Hospital, Paris

SUMMARY The efficacy and safety of cyclosporin A (CyA) for patients with rheumatoid arthritis were assessed in a four month double blind, placebo controlled study using an initial dosage of 5 mg/kg daily. Six patients withdrew from the study (two in the placebo group because of inefficacy of treatment and four in the CyA group because of side effects). These six patients were considered therapeutic failures. At the end of the trial the study treatment was considered as good or very good by 14 out of the 26 CyA group patients and by only two out of the 26 placebo group patients. Moreover, in the CyA group significant improvement was observed in five of the seven clinical assessment criteria. Clinical improvement was correlated with a decrease in C reactive protein, α_1 glycoprotein levels, and platelet count but not with erythrocyte sedimentation rate or rheumatoid factor titres. Renal toxicity (13 cases) remained the major problem in the management of these patients. This study shows that CyA is effective in active rheumatoid arthritis but requires close monitoring for toxicity.

Key words: clinical trials.

Conventional treatment used in rheumatoid arthritis (RA), i.e., antimalarial drugs, gold salts, and D-penicillamine, has to be discontinued within one year in 50% of the patients with RA because of either ineffectiveness or occurrence of unacceptable side effects.¹ Thus for rheumatologists dealing with RA the search for new drugs is constant.

Cyclosporin A (CyA), a fungal peptide with potent and selective inhibitory activity on T helper activation,^{2,3} is widely used in renal transplantation to prevent graft rejection⁴ and in bone marrow transplantation as a prophylactic against graft v host reaction.⁵ In addition, its efficacy in preventing or decreasing inflammation in immune mediated inflammatory models has been conclusively shown.^{6,7} As T helper activation is an important feature of RA the use of a T cell inhibitor such as CyA in treatment of the disease appeared promising. Open trials had already suggested the efficacy of CyA in refractory RA,^{8–15} and also afforded better knowledge of the monitoring of these patients.

These findings prompted the following ran-

domised double blind, placebo controlled study of CyA in patients with severe adult onset rheumatoid arthritis, using an initial dosage of 5 mg/kg daily and with the possibility of modulating CyA dosage during the trial.

Patients and methods

Fifty two outpatients fulfilling the criteria of the American Rheumatism Association for definite or classic RA¹⁶ were recruited for the study. Other criteria for entry were the presence of active disease defined by at least three of the following: erythrocyte sedimentation rate of 30 mm/1st h or higher, 60 minutes or more of morning stiffness, a Ritchie articular index¹⁷ of 10 or more, a Lee functional index¹⁸ of 5 or more, and at least three joints with effusion or synovitis. Treatment with corticosteroids and non-steroidal anti-inflammatory drugs and/or analgesics was maintained, and their dosages during the trial were noted. Excluded from the study were patients with a serious concomitant medical illness, and/or judged to be in functional class IV by the criteria of the American Rheumatism Association,¹⁹ or with a history of cancer, liver or renal disease, epilepsy, or past or present hypertension even if controlled by medical treatment. Before entering

the trial patients underwent a wash out period of three months for the following drugs: gold, cytotoxic drugs, hydroxychloroquine, D-penicillamine, and all other slow acting investigational or disease modifying drugs. The dose of any orally administered non-steroidal anti-inflammatory drug or corticosteroid had to be stable during the last month before entry into the trial.

STUDY DESIGN

The study was a double blind, placebo controlled trial of four months' duration approved by the ethical review board of Cochin Hospital (Paris). During the trial patients were under the care of two investigators: the first, who was unaware of side effects or safety parameters, recorded the clinical assessment criteria of efficacy at each consultation and, at the end of the trial, rated the effectiveness of treatment. Safety and tolerability were assessed by physical examination (body weight, blood pressure, and pulse rate) and laboratory tests (plasma levels of creatinine and potassium, serum liver enzymes). These parameters were evaluated by a second investigator who could modulate CyA dosage if required. Any concomitant therapy, especially corticosteroids and non-steroidal anti-inflammatory drugs, was noted and given an equivalent score, as previously reported.²⁰

DRUG ADMINISTRATION

CyA and placebo were allocated to patients randomly. They were supplied in coded, unidentifiable, liquid solution for oral administration. After confirming that the patient fulfilled the entry criteria defined above, and after written informed consent was obtained, the study drug was supplied according to a randomisation scheme. At the start of the study both investigators were unaware of the meaning of the randomisation code. The investigator who evaluated the efficacy parameters remained unaware of the code meaning until the last patient had completed the study.

Patients received the study drug twice daily. The initial dosage was 5 mg/kg/day for all patients except for those concurrently taking cimetidine, for whom the initial dosage was 2.5 mg/kg/day. This was reduced by half if renal toxicity appeared (defined as more than 50% increase in plasma creatinine level over baseline or plasma creatinine level >150 µmol/l, or both). In such cases plasma creatinine was assessed one week after CyA dosage reduction and the CyA dosage was again reduced by half if renal toxicity persisted. If it did not disappear within one week after the second dosage reduction, CyA was discontinued. Hypertension, defined by the detection (during two consecutive consultations) of a

diastolic pressure >95 mmHg and a systolic pressure >150 mmHg in 18–50 year old patients and by a diastolic pressure >100 mmHg and a systolic pressure >160 mmHg in 50–75 year old patients, was treated according to standard practice. If treatment was inefficient within two weeks the study drug was reduced by half and discontinued if hypertension did not disappear within one week after dosage reduction.

After one month of therapy, if clinical efficacy (evaluated by the monthly overall assessment of the patient) had not been achieved, the dosage was increased by 1 mg/kg/day.

CLINICAL ASSESSMENT

The clinical assessment, made twice during the first month and monthly during the next three months, included the following: (a) severity of pain evaluated by the use of a 100 mm visual analogue scale and by the Ritchie articular index¹⁷; (b) degree of inflammation assessed by the latent period before the resolution of early morning stiffness, the use of a score of swollen joints as previously reported,²¹ and the proximal interphalangeal circumference (total of 10 joints); (c) functional impairment estimated by grip strength (average in mmHg of three consecutive measurements on each side) and the use of the Leff functional index¹⁸; (d) the overall assessment evaluated monthly by the patient, comparing his or her own state with that at the previous examination (+3=much better, +2=better, +1=a little better, 0=no change, -1=a little worse, -2=worse, -3=much worse) and at the end of the trial by patients and the blind investigator, who noted the efficacy of the treatment as nil, mild, moderate, good, or excellent. Nil, mild, and moderate efficacy were taken to indicate therapeutic failure. This parameter was considered the most important in analysing the trial.

LABORATORY ASSESSMENT

Laboratory assessment (according to standard methods) was made at the start of the trial and at each examination and included the following evaluations: routine haematological variables, Westergren sedimentation rate, plasma creatinine level, uric acid, potassium, serum aspartate alanine transferase, alkaline phosphatase, C reactive protein and α_1 glycoprotein. Determination of rheumatoid factor titres by the diluted latex and by the Waaler-Rose tests was carried out at the start of the trial, after two months, and at the end of the trial.

STATISTICAL ANALYSIS

Statistical analyses were carried out to assess the effects of CyA on all patients entering the study and

to assess improvement in those patients who continued treatment until the end of the study. Owing to the non-normal distribution of many of the response variables, statistical analyses were made with non-parametric tests. Changes in the variables between the start and the end of the trial in each treatment group were compared by the non-parametric Mann-Whitney U test. The threshold of significance adopted was 5% (two tailed).

Results

PATIENTS AND STUDY COURSE

Table 1 summarises patient characteristics at the start of the trial. There was no significant difference of demographic data or the clinical and laboratory variables measured between the two groups. At entry six patients (four in the CyA group) had

Table 1 Baseline characteristics of the 52 patients with rheumatoid arthritis studied

Characteristics	Cyclosporin	Placebo
Number of patients	26	26
Age (years)*	57.5 (50.7-60.7)	57.5 (51.1-60.5)
Sex (F/M)	23/3	24/2
Disease duration (years)*	8.0 (11.3-14.7)	15.0 (11.4-20.0)
Previous SAARDs†		
Gold	25	24
D-Penicillamine	22	20
Hydroxychloroquine	18	22
Immunosuppressive drugs	5	3
Number seropositive (diluted latex reaction or Waller-Rose)	20	22
HLA-DR4 (+/-)	14/12	10/16
Corticosteroid consumption‡ (mg/day)	n=21 10.0 (7.3-11.3)	n=22 10.0 (7.7-10.2)

*Values are median (95% confidence interval).
†SAARDs=slow acting antirheumatic drugs.
‡Values are number of patients taking corticosteroids and median (95% confidence interval).

plasma creatinine levels of over 100 µmol/l; they were kept in the study. Six of the 52 patients dropped out of the trial, two in the placebo group owing to treatment inefficacy at month 3, and four in the CyA group because of side effects. Over the study period there were no significant changes either in the daily dose of prednisolone (confidence interval from 7.3-11.3 mg/day at entry to 6.5-10.0 at month 4 in the CyA group and from 7.7-10.2 to 7.2-9.4 in the placebo group) or in the daily score of non-steroidal anti-inflammatory drugs (confidence interval from 6.5-13.6 to 4.6-11.5 in the CyA group and from 6.2-11.6 to 5.8-11.8 in the placebo group).

OVERALL ASSESSMENT OF TREATMENT
The overall efficacy of treatment was assessed by all patients included in the trial; the six patients who had to stop treatment were considered as therapeutic failures regardless of the reason for stopping treatment. Treatment was evaluated as effective by 14/26 (54%) of the patients taking CyA compared with 2/26 (8%) of those taking placebo (p <0.0001) (Table 2).

DETAILED ANALYSIS OF RESPONSE TO TREATMENT
This analysis was undertaken in the 46 patients who completed the trial. Table 3 shows the changes that had occurred in each variable at the end of the trial. All clinical variables showed greater improvement in the patients receiving CyA than in those receiving placebo, with a significant difference in all clinical variables except for grip strength and Ritchie index, though the trend was favourable for the latter (p=0.057).

This clinical improvement was correlated with biological parameters, i.e., decrease in platelet count, in α₁ glycoprotein, and C reactive protein levels. Erythrocyte sedimentation rate and rheumatoid factor titres, however, remained unchanged. The proportion of patients showing improvement can be evaluated by the overall judgment of the patient or the investigator, but it can also be

Table 2 Overall assessment at the end of the trial

Efficacy evaluated by:	Treatment	Efficacy of treatment*					p Value
		Nil	Mild	Moderate	Good	Very good	
Patient	Cyclosporin	5(4)	4	3	9	5	0.006
	Placebo	14(2)	5	5	2	0	
Investigator	Cyclosporin	5(4)	4	6	8	3	0.03
	Placebo	14(2)	4	6	2	0	

*Values are numbers of patients; numbers of patients dropping out of the trial are given in parentheses.

assessed by the proportion of patients showing substantial (>50%) improvement in some selected clinical variables. Such an improvement was observed for morning stiffness in 17 of the 22 CyA group patients and in only seven of the 24 placebo group patients; in five of the 22 CyA group patients and in three of the 24 placebo group patients for Ritchie articular index; in 11 of the 22 CyA group patients and in four of the 24 placebo group patients with regard to the number of swollen joints; and in six of the 22 CyA group patients and in three of the 24 placebo group patients with regard to the Lee functional index. Calculation of the proportion of patients with improvement is highly dependent on the absolute value of the variable at baseline. This explains differences in the proportion of patients with improvement across the four variables. The effects of treatment (differences in percentage improvement between treatment and control groups), however, are similar across these outcome measurements and are consistent with a beneficial effect of CyA.

LATENT PERIOD BEFORE CyA ACTIVITY

The latent period before the beginning of CyA activity was estimated by detailed analysis of changes over time of some of the clinical variables (Fig. 1). All results in the two groups diverged only from the second month of treatment.

ASSESSMENT OF ACCEPTABILITY OF TREATMENT

Numerous adverse reactions occurred during the trial and resulted in withdrawal of four patients (Table 4).

Hypertrichosis (eight cases) was moderate in seven patients and more severe in one, necessitating depilation after 4 months.

Gingival hyperplasia (three cases) was asymptomatic in two patients but was associated with local pain and gingival haemorrhage during tooth brushing in one case.

Nausea (eight cases in the CyA group) was moderate and transient, occurring during the first two or three weeks of treatment in seven cases.

Table 3 Clinical and biological variables at start of treatment and after four months' therapy of the 46 patients with rheumatoid arthritis who completed the trial (22 in the cyclosporin group, 24 in the placebo group)

Variables	Before therapy		After therapy		Difference from baseline†		p Value
	Cyclosporin	Placebo	Cyclosporin	Placebo	Cyclosporin	Placebo	
Clinical							
Pain (VAS)§	61.5‡ (48.8, 71.1)	56.0 (52.5, 71.2)	44.0 (30.0, 53.1)	61.0 (48.5, 68.9)	-14.0 (-30.7, -6.1)	-1.0 (-11.8, 5.4)	0.048
Ritchie index	18.0 (15.9, 24.0)	20.0 (17.3, 25.5)	16.5 (11.1, 19.0)	21.5 (17.0, 25.7)	-6.0 (-8.4, -1.4)	0.50 (-3.5, 3.4)	0.057
Morning stiffness (min)	120.0 (98.8, 208.9)	90.0 (81.3, 194.5)	30.0 (11.5, 80.2)	75.0 (69.3, 183.2)	-75.0 (-157.8, -58.3)	0 (-73.4, 50.0)	0.003
Global score of swollen joints	16.0 (11.9, 21.1)	12.5 (11.4, 20.3)	8.0 (6.7, 14.6)	17.0 (13.2, 22.7)	-5.0 (-9.3, -2.6)	-0.50 (-2.0, 6.3)	0.007
PIP§ circumference (mm, total of 10 joints)	580.0 (555.2, 599.3)	572.0 (555.0, 580.4)	580.5 (552.3, 594.6)	579.0 (560.9, 586.1)	-5.5 (9.0, 1.4)	1.5 (0.0, 11.6)	0.011
Grip strength (mmHg)	69.5 (44.4, 90.4)	46.0 (40.4, 110.0)	81.5 (49.6, 118.6)	44.5 (41.8, 112.3)	7.50 (-4.7, 38.1)	0.0 (-15.6, 19.4)	NS
Lee functional index	12.0 (9.8, 13.7)	9.5 (7.5, 12.1)	6.5 (5.9, 9.8)	9.5 (7.1, 11.5)	-4.0 (-5.2, -2.6)	-1.0 (-2.2, 1.3)	0.004
Monthly patient's overall assessment	—	—	—	—	2.0 (0.7, 3.2)	0.0 (-1.7, 0.8)	0.014
Biological							
ESR§ (mm/1st h)	50.0 (42.9, 72.0)	36.5 (30.0, 50.6)	48.0 (36.3, 60.8)	37.5 (31.7, 49.9)	-2.0 (-21.5, 3.7)	0.5 (-7.9, 8.9)	NS
Platelets×10 ⁻⁹ /l	423 (363, 503)	395 (335, 462)	336 (317, 452)	432 (373, 497)	-51.0 (-89, 4)	8.5 (-7, 80)	0.011
α ₁ Glycoprotein (g/l)	1.9 (1.8, 2.0)	1.8 (1.6, 1.9)	1.5 (1.4, 1.8)	1.8 (1.6, 1.9)	-0.37 (-0.54, 0.19)	0.0 (-0.19, 0.12)	0.012
C reactive protein (mg/l)	26.5 (23.1, 47.6)	27.9 (20.0, 40.3)	15.2 (9.2, 28.7)	27.3 (19.9, 46.4)	-10.5 (-26.8, -2.0)	0.0 (-9.0, 23.1)	0.052

*Statistical significance determined by the non-parametric Mann-Whitney U test.

†The median of the difference is not necessarily equal to the difference between medians.

‡Values are median (95% confidence interval).

§VAS=visual analogue scale (100 mm long); PIP=proximal interphalangeal; ESR=erythrocyte sedimentation rate.

Fig. 1 Mean change over time of certain variables in the group given placebo (---) and the group given cyclosporin (—).

was severe and associated with vomiting in one case, necessitating the discontinuation of treatment at day 10.

Eight patients in the CyA group complained of paraesthesia of hands and feet occurring for 5–10 minutes, two to three times a week. This side effect was observed at the beginning of treatment and

resolved spontaneously, except in one patient, who was extremely incapacitated and had to discontinue treatment at day 43. Paraesthesia resolved spontaneously three days after CyA discontinuation in this patient.

Plasma creatinine level rose from 81 to 105 $\mu\text{mol/l}$ in the CyA group but remained unchanged in the placebo group at 80 $\mu\text{mol/l}$ ($p < 0.0001$). The mean rise in plasma creatinine level was 26% after four months of therapy in the CyA group. A rise in plasma creatinine level of more than 50% of the baseline value or more than 150 $\mu\text{mol/l}$ was observed in 13 patients receiving CyA but resulted in withdrawal in only one case. This side effect was observed at day 15 (two cases), 30 (three cases), 60 (two cases), 90 (five cases), and 120 (one case). In the CyA group it was observed in two of the three patients who were concurrently taking cimetidine and in three of the four patients in whom the plasma creatinine level was more than 100 $\mu\text{mol/l}$ at the start of the study. In the patient who discontinued CyA at month 1 the plasma creatinine level rose from 134 $\mu\text{mol/l}$ at the start to 159 $\mu\text{mol/l}$ at day 30 and decreased to 115 $\mu\text{mol/l}$ three months after CyA withdrawal.

In the 12 other cases where increased plasma creatinine level was noted it returned to basal value

Table 4 Type and frequency of side effects in the treatment groups

Side effects	Cyclosporin group (n=26)	Placebo group (n=26)
Renal toxicity*	13 (1)†	0
Hypertension	0	1
Gingival hyperplasia	3	0
Hypertrichosis	8	1
Paraesthesia	8 (1)	3
Nausea	8 (1)	3
Gastric ulceration	1 (1)	0
Dyspepsia	2	2
Mammary hypertrophy	1	0
Rise in postassium level ($>5 \mu\text{mol/l}$)	2	1

*Increase in plasma creatinine level ($>50\%$ over baseline value or $>150 \mu\text{mol/l}$).

†Figures in parentheses indicate numbers of patients dropping out of the trial because of side effects.

within one week after CyA dosage reduction. Disease activity recurred in six of these patients. CyA dosage was again increased without recurrence of renal toxicity in four patients. Mean (SD) CyA dosage was 4.0 (1.6) mg/kg daily after four months of therapy in the 11 patients who had to reduce CyA intake and who completed the trial (one of the 12 patients withdrew because of gastric ulceration). At the final visit nine of these 13 patients were considered as therapeutic successes.

Hypertension, as previously defined, was not observed in this study, though an increase in systolic and diastolic blood pressure was observed in the CyA group (from 135 to 147 mmHg ν a constant value of 136 mmHg in the placebo group, $p=0.08$ and from 80 to 83 mmHg ν a constant value of 80 mmHg in the placebo group, $p=0.34$ respectively).

DRUG DOSAGE DURING THE TRIAL

At entry there was no significant difference in the dosage of the study drug according to treatment group. Owing to inefficacy of the drug, the dosage was increased from 4.6 (SD 0.9) mg/kg daily at entry to 6.5 (0.5) mg/kg daily at the final visit in the placebo group, but was unchanged in the CyA group (from 4.6 (0.9) to 4.6 (1.8)). In the CyA group, however, the dosage range after four months was large (from 1.2 to 7.5 mg/kg daily). This wide range was explained by the modulation of CyA during the trial with, on the one hand, CyA dosage reductions because of renal toxicity, and, on the other hand, increases in CyA dosage because of inefficacy after one month of therapy. After four months of therapy the CyA dose was the same in all CyA patients irrespective of clinical assessment, i.e., 4.6 (2.4) mg/kg daily in patients considering the treatment as good or very good ν 4.6 (1.4) in the others.

Discussion

Open uncontrolled studies have suggested the efficacy of CyA in RA.⁸⁻¹⁵ In an open controlled study comparing CyA with azathioprine Forre *et al* reported a tendency towards greater improvement in the CyA group than in the azathioprine group.²² CyA efficacy was confirmed in a double blind, placebo controlled trial, but the high number of drop outs in both groups (eight out of the 17 CyA group and six of the 19 placebo group) precluded any definitive conclusion.²³ These trials, however, extended our knowledge of the monitoring of such treatment. In the present study the selected inclusion criteria, dosage schedule, and monitoring of patients were based on this previous experience: initial dosage of 5 mg/kg/day rather than 10 mg/kg daily, close monitoring of plasma creatinine level

and reduction by half of the CyA dosage in the case of an increase of more than 50% over baseline above 150 μ mol/l, or both, exclusion of patients with past or present hypertension, lower initial dosage in patients concurrently taking cimetidine, preventive local therapy for gingivitis (frequent tooth brushing, treatment of possible tooth decay). CyA plasma determinations were not used to monitor patients, which is at variance with the recommendations of Von Graffenried and Harrison.²⁴

In addition, these previous reports prompted us to conduct a double blind trial that included two investigators. Only this method affords objective evaluation of clinical modifications as changes in plasma creatinine levels are relatively common during CyA therapy. One might think that hypertrichosis could hamper the study design. In fact, in this study, although eight of the 26 patients in the CyA group complained of hypertrichosis, this side effect was noticed in only two cases by the blind investigator. More important is the fact that using this method, CyA dose modulation was possible. Thus the 13 patients with an increase in plasma creatinine level occurring during the trial were not excluded from follow up but were closely monitored by the non-blind investigator. This is of clinical importance as (a) only one patient had to withdraw from the study because of renal toxicity, (b) nine of the 13 patients in whom renal toxicity occurred were finally considered therapeutic successes.

This present study confirms the efficacy of CyA in the treatment of active rheumatoid arthritis. The clinical parameters evaluating pain, inflammation, and functional impairment improved in the CyA group compared with the placebo group. Variations among individuals were noted in the CyA dosage required to achieve clinical improvement. Detailed analysis of changes in clinical variables over time showed that CyA seemed to act as early as the second month of treatment. Clinical improvement correlated with a decrease in C reactive protein, α_2 glycoprotein levels, and platelet count. In contrast, erythrocyte sedimentation rate remained unchanged after CyA therapy. The absence of modification or even an increase in erythrocyte sedimentation rate has been previously noted during CyA therapy in RA²² and in other diseases.²⁵ This phenomenon remains unexplained.

We observed numerous side effects, as previously reported by others.²⁵ The frequency or the severity, or both, of nausea, gingivitis, hypertrichosis, and hypertension, however, seemed to be lower in the present study as they resulted in therapeutic withdrawals in only four out of the 26 patients in the CyA group. These discrepancies may be explained by the low initial dosage, the exclusion of patients

with previous hypertension, and the attention paid to dental care. Renal toxicity remained the major problem in the management of CyA treated RA. Increased plasma creatinine levels in two of the three patients concurrently taking cimetidine confirm our previous report¹⁴ and suggest that this drug combination may be nephrotoxic.²⁶ Moreover, this side effect was observed in three of the four patients in whom the plasma creatinine level was over 100 $\mu\text{mol/l}$ at entry visit. These data and the increased occurrence of CyA nephrotoxicity in RA compared with other diseases²⁴ suggest that either the non-steroidal anti-inflammatory drugs used in RA or the kidney involvement associated with the disease²⁷ may contribute to CyA nephrotoxicity.

The clinical benefit of a drug is more difficult to assess as it depends on the benefit/risk ratio. In this study of four months' duration including generally active patients with RA who had previously failed to improve with conventional slow acting drugs, CyA seemed to be of clinical benefit. Longer term studies are necessary to determine whether treatment with CyA will remain of clinical benefit as the long term renal tolerance of CyA is not yet known and previous studies have shown disease recurrence within several weeks of CyA discontinuation.¹⁴ Such studies have to be carefully conducted as we do not yet know whether the histological renal lesions induced by CyA are related to the duration of the treatment.

Cyclosporin was kindly provided by Sandoz, France. The blood concentrations of C reactive protein and α_1 glycoprotein were determined by Dr L Moachon (Paris, France). The authors are greatly indebted to V Figeac for helpful secretarial assistance.

References

- Amor B, Herson D, Cherot A, Delbarre F. Polyarthritides rhumatoïdes évoluant depuis plus de 10 ans (1966-1978): analyse de l'évolution et des traitements de 100 cas. *Ann Med Interne (Paris)* 1981; **132**: 168-73.
- Bunjes D, Hardt C, Rüllinghoff M, Wagner H. Cyclosporin A mediates immunosuppression of primary cytotoxic T cell responses by impairing the release of interleukin 1 and interleukin 2. *Eur J Immunol* 1981; **11**: 657-61.
- Borel J F, Lafferty K J. Cyclosporin: speculation about its mechanism of action. *Transplant Proc* 1983; **15**: 1881-5.
- Land W, Castro L A, White D J G, et al. Cyclosporin in renal transplantation. In: Borel J F, ed. *Cyclosporin*. Basel: Karger, 1986: 293-328.
- Gratwohl A, Sopeck B. Bone marrow transplantation with cyclosporin. In: Borel J F, ed. *Cyclosporin*. Basel: Karger, 1986: 404-31.
- Henderson B, Staines N A, Burrai I, Cox J H. The anti-arthritis and immunosuppressive effects of cyclosporin on arthritis induced in the rat by type II collagen. *Clin Exp Immunol* 1984; **57**: 51-6.
- Jones M G, Harris G. Prolongation of life in female NZB/NZW (F1) hybrid mice by cyclosporin A. *Clin Exp Immunol* 1985; **59**: 1-9.
- Hermann B, Müller W. Die therapie der chronischen polyarthritiden mit Cyclosporin A, einem neuen immun-suppressivum. *Aktuelle Rheumatologie* 1979; **4**: 173-86.
- Graf U, Marbet U, Müller W, Thiel G. Cyclosporin A: effects and side effects in the treatment of rheumatoid arthritis and psoriatic arthritis. *Immun Infekt* 1981; **9**: 20-8.
- 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.
- 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.
- Herog Ch, Gross D. Low dose cyclosporin A and prednisone: a step in the direction of selective immunosuppression in rheumatoid arthritis refractory of treatment (6-month follow-up). In: Schindler R, ed. *Cyclosporin in autoimmune diseases*. Berlin: Springer, 1985: 289-96.
- Madhok R, Capell H A. Cyclosporin in rheumatoid arthritis: preliminary results. In: Schindler R, ed. *Cyclosporin in autoimmune diseases*. Berlin: Springer, 1985: 297-8.
- Dougados M, Amor B. Cyclosporin A in rheumatoid arthritis: preliminary clinical results of an open trial. *Arthritis Rheum* 1987; **30**: 83-6.
- Weinblatt M E, Coblyn J S, Fraser P A. Cyclosporin: a treatment of refractory rheumatoid arthritis. *Arthritis Rheum* 1987; **30**: 11-17.
- Ropes M W. Diagnostic criteria for rheumatoid arthritis. 1958 revision. *Ann Rheum Dis* 1959; **18**: 49-53.
- Ritchie D M, Boyle J A, McInnes J M, Grieson 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.
- 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.
- Steinbrocker O, Traeger C H, Batterman R C. Therapeutic criteria in rheumatoid arthritis. *JAMA* 1949; **140**: 659-62.
- Dougados M, Boumier P, Amor B. Sulphasalazine in ankylosing spondylitis: a double blind controlled study in 60 patients. *Br Med J* 1986; **293**: 911-4.
- Amor B, Mery C, Gery A, de. Thiopronin (N-(2-mercaptopropionyl)glycine) in rheumatoid arthritis. *Arthritis Rheum* 1982; **25**: 698-703.
- Forre O, Bjerkhoel F, Salvesen 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.
- Van Rijthoven A W A M, Dijkmans B A C, Goei The H S, et al. Cyclosporin treatment for rheumatoid arthritis: a placebo controlled, double blind, multicentre study. *Ann Rheum Dis* 1986; **45**: 726-31.
- Von Graffenried B, Harrison W B. Cyclosporin in autoimmune diseases: side effects (with emphasis on renal dysfunction) and recommendations for use. In: Schindler R, ed. *Cyclosporin in autoimmune diseases*. Berlin: Springer, 1985: 59-73.
- Palestine A G, Nussenblatt R B, Chan C. Side effects of systemic cyclosporin in patients not undergoing transplantation. *Am J Med* 1984; **77**: 652-5.
- Jarowenko M V, Van Buren C T, Kramer W G, Lorber M I, Flechner S M, Kahan B D. Ranitidine, cimetidine and the cyclosporin treated recipient. *Transplantation* 1986; **42**: 311-2.
- Breedveld F C, Valentijn R M, Westedt M L, Weening J J. Rapidly progressive glomerulonephritis with glomerular crescent formation in rheumatoid arthritis. *Clin Rheumatol* 1985; **4**: 353-9.