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Cyclosporin treatment for rheumatoid arthritis: a placebo controlled, double blind, multicentre study

A W A M VAN RIJTHOVEN,[1] B A C DIJKMANS,[2] H S GOEI THE,[3] J HERMANS,[4] Z L M B MONTNOR-BECKERS,[1] P C J JACOBS,[3] AND A CATS[2]

From the [1]Department of Rheumatology, Deaconess Hospital, Eindhoven; the [2]University Hospital, Leiden; the [3]De Wever Hospital, Heerlen; and the [4]Department of Medical Statistics, University, Leiden, The Netherlands

SUMMARY The efficacy and safety of cyclosporin for patients with rheumatoid arthritis (RA) were assessed in a six month double blind, placebo controlled, multicentre study. The initial dosage of the drug was 10 mg/kg daily for two months. There were many discontinuations in both the cyclosporin group (eight out of 17) and the placebo group (six out of 19). Of the patients who completed the six months of therapy, those who had received cyclosporin showed a significant improvement in the number of swollen joints, the Ritchie articular index, and pain at active movement and at rest, compared not only with their condition at the start of the study, but also with the end results of the placebo group. Major adverse reactions to the drug were gastrointestinal disturbances and nephrotoxicity, which were probably due to the relatively high dosages of cyclosporin given in combination with non-steroidal anti-inflammatory drugs.

The treatment of patients with rheumatoid arthritis (RA) is a challenging problem for rheumatologists. Several clinical studies have shown that antimalarials, gold salts, D-penicillamine, and some cytostatic agents have disease activity modifying properties,[1–4] but the response to treatment with these drugs is variable and a certain proportion of the RA patients do not benefit. These unresponsive patients are considered to have refractory RA, an intriguing but daunting problem to the practising clinician.

Cyclosporin is a fungal peptide with unique immunosuppressive properties, inhibiting activation of both B and T lymphocytes and certain macrophage functions.[6] In the clinical situation the activity of cyclosporin is highest when the drug is administered during the inductive phase of an immune response (sensitisation), i.e., at the time of organ transplantation. In animal models of autoimmune diseases, however, i.e., after sensitisation, cyclosporin also suppresses the effector phase.[7] Although its action has been reported to be reversible, studies on experimental arthritis in rats suggest a long lasting effect of this drug.[8]

These findings and the favourable results of cyclosporin treatment of other autoimmune diseases in man[9 10] led us to perform a double blind, placebo controlled, multicentre study to evaluate the efficacy and safety of this drug in patients with refractory RA.

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Correspondence to Professor A Cats, Department of Rheumatology, University Hospital, Building 1, C2Q, PO Box 9600, 2300 RC Leiden, The Netherlands.

Patients and methods

Patients with active and erosive definite or classical RA, according to the American Rheumatism Association criteria, and who had previously been treated with antimalarials and gold salts or D-penicillamine were included in the study. Further criteria for entry were anatomical and functional stage II or III[11] and termination of corticosteroid therapy at least six months before the start of the study. Patients who had a history of cancer, a serious concomitant illness, abnormal liver or renal function, or both, extra-articular manifestations of RA other than nodules, or who had undergone joint surgery within the preceding three months were excluded. Other exclusion criteria were: a white cell count of less than 3000/mm^3 (3×10^9/l), a platelet

count below 100 000/mm^3 (100×10^9/l), and concomitant therapy with potentially nephrotoxic drugs except non-steroidal anti-inflammatory agents.

After their informed consent had been obtained the patients were allocated randomly to either the oral cyclosporin or the placebo group, each centre having a separate list of the random allocations. The initial cyclosporin dosage was 10 mg/kg once a day given at noon for two months. If there was a satisfactory response the dosage was reduced to 7·5 mg/kg once a day (months 3 and 4) and then to 5 mg/kg once a day (months 5 and 6). The dosage was adjusted according to clinical response and side effects. Furthermore, patients were monitored on the basis of trough blood levels of cyclosporin. Blood samples for the measurement of these concentrations were drawn into heparinised tubes and stored at 4°C for at most one week before the cyclosporin levels were determined in whole blood by a radioimmunoassay[12] performed with the kit supplied by Sandoz. If the trough blood level of cyclosporin exceeded 1000 ng/ml the dosage was adjusted, and the same volume reduction was made in the paired patient in the placebo group. In both groups administration was stopped after six months.

Non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed according to individual need. In each centre one rheumatologist, who was not aware of side effects or safety parameters, assessed the joints of each of the patients of that centre monthly. The parameters of efficacy determined monthly were as follows: the duration of morning stiffness, the number of swollen joints, the Ritchie index, pain at active movement and at rest, and grip strength measured with a vigorimeter. Radiographs of hands, wrists, and feet were made at entry and after six months. Radiological abnormalities of the metacarpophalangeal and metatarsophalangeal joints and the proximal interphalangeal joints of hands and feet were graded from 0 to 4 (grade 0: no abnormalities; grade 1: dubious erosions; grade 2: definite but mild erosions or narrowing of the joint space; grade 3: more destructive changes; and grade 4: severe erosions or ankylosis[13]), and the sum of these abnormalities was called the radiological score.

After one week and six months of cyclosporin therapy a global assessment of efficacy was made by the patient and the investigator, both of whom also made an overall assessment of efficacy at the end of the study (grades: grade 0: no effect; grade 1: slight improvement; grade 2: moderate improvement; grade 3: good improvement; grade 4: excellent improvement).

Safety and tolerability were assessed by physical examination (body weight, blood pressure, and pulse rate) and laboratory tests (cyclosporin blood levels, serum levels of creatinine and potassium, liver enzymes); these parameters were evaluated by a second doctor in each centre who was not involved in the assessment of efficacy parameters.

Table 1 *Characteristics of the 36 rheumatoid arthritis patients after random allocation to the cyclosporin and placebo groups*

Parameter	*Cyclosporin group (n=17)*	*Placebo group (n=19)*
Sex	13 F/4 M	15 F/4 M
Age (years)	54·5 (12·9; 24–69)*	55·3 (9·7; 37–68)
Duration of illness (years)	11·8 (6·2)	14·5 (11·3)
Functional stage	II (n=12)	II (n=10)
	III (n=5)	III (n=9)
Anatomical stage	II (n=6)	II (n=8)
	III (n=11)	III (n=11)

*mean (SD; range).

Table 2 *Kind and frequency of side effects in both groups of rheumatoid arthritis patients in the present study*

Side effects	*Cyclosporin group (n=17)*	*Placebo group (n=19)*
Gastric pain	5	2
Nausea	9	3
Vomiting	3	0
Rise of serum creatinine level	13	5
Hyperkalaemia	1	0
Urine retention	1	0
Hirsutism	3	0
Tremor	2	0
Gingival hyperplasia	3	0
Hyperaesthesia	5	1
Headache	0	4

Table 3 *Time of and reason for discontinuation of cyclosporin or placebo administration during the present study*

Group	*Reason*	*Time (weeks)*
Cyclosporin	Hyperkalaemia	6
	Non-compliance	6
	Gastrointestinal intolerance, raised serum creatinine level	6
	Gastrointestinal intolerance	6
	Gastrointestinal intolerance	8
	Gastrointestinal intolerance	8
	No effect	12
	Rise of serum creatinine level	19
Placebo	No effect	2
	No effect	8
	No effect	8
	No effect	10
	No effect	16
	Duodenal ulcer	20

Table 4 *Clinical and laboratory parameters of efficacy of treatment in both groups of rheumatoid arthritis patients in the present study*

Parameter	*Cyclosporin group*						*Placebo group*						*p Value**
	At time 0			*At six months*			*At time 0*			*At six months*			
Morning stiffness (min)	69	(43)†	(n=17)‡				68	(56)	(n=18)				
	58	(32)	(n=9)§	56 NS‖	(78)	(n=8)	52	(43)	(n=13)	47 NS‖	(43)	(n=13)	NS
Number of swollen joints	10·5	(2·8)	(n=17)				9·1	(3·3)	(n=19)				
	10·3	(2·5)	(n=9)	3·8 p=0·01	(4·8)	(n=9)	8·3	(3·0)	(n=13)	6·1 NS	(2·7)	(n=13)	0·02
Ritchie index	22·2	(8·1)	(n=17)				22·9	(8·0)	(n=19)				
	23·6	(8·1)	(n=9)	11·1 p=0·01	(5·8)	(n=9)	21·3	(6·9)	(n=13)	18·3 NS	(6·5)	(n=13)	0·03
Pain on active movement	2·4	(0·6)	(n=17)				2·2	(0·7)	(n=19)				
(score range: 0–3)	2·4	(0·7)	(n=9)	1·6 p=0·01	(1·0)	(n=9)	2·0	(0·6)	(n=13)	2·2 NS	(0·7)	(n=13)	0·01
Pain at rest	1·5	(1·2)	(n=17)				1·1	(0·9)	(n=19)				
(score range: 0–3)	1·3	(1·3)	(n=9)	0·6 p=0·01	(0·9)	(n=9)	0·9	(0·8)	(n=13)	1·1 NS	(1·0)	(n=13)	0·07
Erythrocyte sedimentation rate													
(ESR) (mm/1st h)	59	(40)	(n=16)				58	(31)	(n=19)				
	65	(42)	(n=8)	50 NS	(24)	(n=9)	44	(23)	(n=13)	58 p=0·05	(25)	(n=13)	NS
Radiological score	96	(38)	(n=17)				86	(43)	(n=19)				
	105	(33)	(n=9)	115 NS	(40)	(n=9)	87	(41)	(n=13)	102 NS	(40)	(n=13)	NS

*For comparison of the two groups with respect to their differences between the start and end of the study.
†Mean (SD).
‡Number of patients.
§Number of patients assessed up to six months.
‖Difference within the groups between start and end of the study.

The Wilcoxon two sample test was used for statistical analysis of the data for comparison of the two groups, and the signed rank test was applied for analysis within the groups.

Results

Thirty six patients (28 women and eight men, mean age 54·9 years, SD 11·2, range 24–69 years) were admitted to the study. The cyclosporin group comprised 17 patients and the placebo group 19; the demographic characteristics of the patients, which are shown in Table 1, indicate an equal distribution over the groups. During the trial the frequency of side effects was considerable in both groups (Table 2). The cyclosporin group showed a highly significant ($p<0·005$) rise of the serum creatinine level relative to the pretreatment values, the mean values for the group being 98·7 (SD 31·4) and 72·6 (SD 18·2) μmol/l, respectively; in two patients the rise of the serum creatinine level was judged unacceptable for continuation of cyclosporin administration (Table 3). Other reasons for withdrawing the drug in the cyclosporin group were gastrointestinal intolerance in four patients and absence of effect, hyperkalaemia, and lack of compliance, each in one patient (Table 3). In the placebo group administration was stopped in five patients because of lack of effect and in one patient who developed a duodenal ulcer (Table 3).

The findings concerning clinical, laboratory, and radiological efficacy parameters for the two groups are given in Table 4. Statistical analysis disclosed that at the start of the study the groups were comparable for each of the efficacy parameters. Further analysis was restricted to the patients who completed the six months of therapy. Comparison of the changes in both groups during the study showed significant improvement for the cyclosporin group with respect to the number of swollen joints, the Ritchie index, and pain on active movement, and pain at rest showed borderline significance (Table 4). The changes in efficacy parameters within the groups over the same period are also shown in Table 4.

As these data indicate, in the placebo group no improvement occurred in any of the parameters and the ESR was significantly higher at six months than at the start of the study. The cyclosporin group showed a non-significant decrease of the sedimentation rate (from 65 mm to 50 mm after one hour), significant improvement in the number of swollen joints, Ritchie index, and pain at both active movement and rest at six months and also less radiological progression of joint destruction, but this last was not significant relative to the placebo group.

The other parameters of efficacy and safety are given in Table 5. At the end of the study period the values for grip strength did not differ either between or within the groups. The mean score for global

Table 5 *Other efficacy and safety parameters assessed in patients with rheumatoid arthritis in the present study*

Parameter	*Cyclosporin group*					*Placebo group*					*p Value**
	At time 0		*At six months*			*At time 0*		*At six months*			
	(n= 9)					*(n=13)*					
Grip strength (Kpa)											
Left hand	11·3	(9·2)†	13·7	(12·4)	NS‡	15·9	(10·0)	15·1	(9·4)	NS	NS
Right hand	12·9	(11·2)	15.0	(14·3)	NS	17·5	(10·9)	17·2	(12·7)	NS	NS
Global efficacy (score range: 0–4)											
Patient	0·6	(1·0)§	1·8	(1·3)	0·07	0·4	(0·7)	0·6	(1·0)	NS	NS
Investigator	0·3	(0·7)§	1·9	(1·3)	0·02	0·3	(0·6)	0·5	(0·7)	NS	0·01
Overall efficacy (score range: 0–4)											
Patient			2·5	(1·1)				1·1	(1·3)		0·07‖
Investigator			2·8	(0·9)				0·7	(1·0)		0·01‖
Haemoglobin (mmol/l)	7·9	(1·0)	7·7	(0·9)	NS	7·9	(1·0)	7·6	(1·1)	NS	NS
Alkaline phosphatase (U/l)	102	(47)	96	(31)	NS	86	(21)	91	(27)	NS	NS
S-Alanine aminotransferase (ALAT) (U/l)	10	(5·1)	9·4	(6·4)	NS	9·6	(4·2)	11·9	(16·1)	NS	NS
Potassium (mmol/l)	4·4	(0·4)	4·6	(0·5)	NS	4·5	(0·3)	4·3	(0·2)	NS	NS

*For comparison of the two groups with respect to their differences between the start and end of the study.
†Mean (SD).
‡Difference within group between start and end of the study.
§Measured after one week of treatment.
‖Difference between the two groups at six months.

efficacy was significantly higher for the cyclosporin group than for the placebo group at six months, as assessed by the investigator. Moreover, the score for the cyclosporin group as assessed by the investigator was significantly higher at the end of the study than at the beginning, but was the same at both time points for the placebo group. At the end of the study the score for overall efficacy as assessed by the investigator was significantly higher for the cyclosporin than the placebo group.

Mean values for haemoglobin, alkaline phosphatase, ALAT, and potassium did not change during the study either between or within the groups.

The mean value for the cyclosporin blood levels of all 17 patients treated with cyclosporin was 675 (SD 223) ng/ml.

Discussion

The main conclusion drawn from the results of this placebo controlled, double blind study is that cyclosporin improves clinically manifest symptoms, i.e., the number of swollen joints, Ritchie articular index, and pain at active movement and at rest, in patients suffering from active rheumatoid arthritis. No significant improvement in morning stiffness or laboratory parameters was found, and the placebo group showed a significant rise of the ESR. This six month study did not yield any evidence that cyclosporin can retard radiographic signs of deterioration. Reduction of radiographic progression of joint destruction, however, is by no means an effect of all 'remittive agents' or disease modifying drugs, and the only available evidence that both gold and cyclophosphamide can retard radiographic deterioration is circumstantial.[14] Cyclosporin may even retain its activity after the inductive phase of the immune response in the clinical situation since it is conceivable that in rheumatoid arthritis sensitisation has already occurred.

The number of withdrawals from the study was high in both groups, but the total of five in the placebo group because of inefficacy suggests that the basis chosen for the selection of patients was good. The improvement of symptoms in the patients with active rheumatoid arthritis treated with relatively high dosages of cyclosporin should, however, be considered in the light of the adverse reactions, i.e., gastrointestinal disturbances and raised serum creatinine levels. This rise in serum creatinine proved partially irreversible (unpublished data), which is not the case for cyclosporin nephrotoxicity in renal allograft recipients.[15 16] It seems probable that the gastrointestinal and nephrotoxic reactions in our patients can be at least partially ascribed to the relatively high dosages of cyclosporin (10 mg/kg as starting dose), which are reflected in the relatively high mean trough blood cyclosporin concentrations. At present it is advised that blood levels higher than 600–800 μg/ml should be avoided for cyclosporin treated patients with an autoimmune disease.[17] Moreover, the concomitant treatment with NSAIDs might have led to gastrointestinal disturbances and nephrotoxicity. Besides nephrotoxicity due to NSAIDs,[18] the kidney in rheumatoid arthritis patients can be directly involved owing to the disease.[19] An increased incidence of disturbances of the upper gastrointestinal tract in rheumatoid arthritis patients has been reported, but it is not clear whether this is related to the drug treatment or represents a systemic manifestation of the disease.[20]

In summary, cyclosporin proved to be more effective than placebo during a six month treatment period in patients with rheumatoid athritis refractory to more conventional drugs. The observed adverse affects may have been dose related and enhanced by concomitant therapy with NSAIDs. Thus cyclosporin seems to be an effective disease modifying drug in rheumatoid arthritis, provided it is given in a daily dose not exceeding 5 mg/kg and is well monitored, with blood trough levels not exceeding 500 ng/ml. Moreover, to avoid nephrotoxicity we recommend the omission of concomitant administration of NSAIDs with the possible exception of sulindac, which is claimed to give less renal dysfunction.[21]

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