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# A RANDOMIZED, DOUBLE-BLIND, 24-WEEK CONTROLLED STUDY OF LOW-DOSE CYCLOSPORINE VERSUS CHLOROQUINE FOR EARLY RHEUMATOID ARTHRITIS

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*Objective.* **To investigate whether low-dose cyclosporin A (CSA) is safe and effective in comparison with chloroquine (CQ) in patients with early rheumatoid arthritis (RA).**

*Methods.* **We performed a randomized, double-blind study comparing CSA with CQ in patients with early RA (duration <2 years) who had had active disease for at least 3 months. Forty-four RA patients with a mean disease duration of 6 months were randomly allocated to receive CSA (initial dosage 2.5 mg/kg/day, maintenance dosage 3.6 mg/kg/day) or CQ (initial dosage 300 mg/day, maintenance dosage 100 mg/day) for 24 weeks.**

*Results.* **Five patients (2 taking CSA and 3 taking CQ) discontinued the study prematurely. Intention-to-treat analysis disclosed a decrease in the swollen joint count by 7 in both groups. The erythrocyte sedimentation rate and C-reactive protein level did not change significantly. CSA and CQ were tolerated equally well, although mild paraesthesia occurred more frequently in the CSA-treated group. The serum creatinine level increased by 13 μmoles/liter (95% confidence interval [95% CI] 4, 22) in the CSA group and by 6 μmoles/liter (95% CI 1, 11) in the CQ group (difference not statistically significant).**

*Conclusion.* **Both CSA and CQ are effective in alleviating the symptoms of active early RA. There is only slightly impaired renal function after 24 weeks of drug administration of either drug in patients with early RA.**

The toxicity and lack of efficacy of conventional disease-modifying antirheumatic drugs (DMARDs) in a considerable proportion of patients with rheumatoid arthritis (RA) (1) justify the continuing search for better treatment modalities. Cyclosporin A (CSA), an immunosuppressive drug that primarily interferes with the function of activated T cells (2), has been proven to alleviate signs and symptoms in intractable (3–6) and advanced (7–9) RA. However, the administration of high doses of CSA to patients with intractable RA was shown to result in renal function disturbances that were partially irreversible (10–12). These irreversible renal function disturbances could be prevented by administering lower doses of CSA and strict monitoring of renal function (7,8,13). Substantial loss of renal function during CSA administration, however, has been demonstrated in all previous studies (3–9,13).

It would appear worthwhile to investigate the potential benefits of CSA in early RA, since activated T cells are thought to be especially important in the early phase of RA, in which T cells might initiate the inflammatory process (14). More importantly, patients with limited disease duration in which the disease itself and nephrotoxic drugs have not yet contributed to nephropathy, may be less sensitive to the development of CSA-related renal function disturbances.

We report the results of a prospective, double-blind, randomized study designed to assess the safety

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and efficacy of CSA, compared with chloroquine (CQ), in patients with early RA.

## PATIENTS AND METHODS

**Patient population and study design.** Patients with RA who fulfilled the American College of Rheumatology 1987 criteria (15) were included in the study after giving informed consent. The inclusion criteria were 1) age between 16 and 65 years, 2) no previous treatment with DMARDs, 3) disease duration of ≤24 months, 4) treatment with an adequate dose of nonsteroidal antiinflammatory drugs (NSAIDs) for at least 3 months, and 5) "active disease" for at least 3 months (at least 3 of the following 4 criteria: ≥3 swollen joints, ≥6 tender joints [spontaneously or on pressure], ≥30 minutes of morning stiffness, and Westergren erythrocyte sedimentation rate [ESR] of ≥28 mm/hour).

Patients were excluded if they had impaired renal function (creatinine clearance <80 ml/minute), hypertension, an active gastric or duodenal ulcer, abnormal liver enzyme levels (more than twice the upper limit of normal), or a history of malignancy or epilepsy. Female patients with childbearing potential who were not practicing adequate contraceptive measures were also excluded.

The double-blind study was for 24 weeks. Patients were randomly allocated to receive CSA or CQ, using the double-dummy system. There were 2 assessors: the primary assessor (RBML) performed the clinical measurements and was blinded to the study medication; the second assessor judged the laboratory parameters for safety.

CQ was given at 300 mg of chloroquine base/day initially, tapered to 200 mg/day after 4 weeks, and after another 4 weeks, to 100 mg/day. This CQ maintenance dose is slightly lower than is generally recommended. We judged the dose schedule as appropriate, based on clinical experience and on studies demonstrating no clinical difference between a high and a low dose of antimalarials (16,17).

The initial CSA dose was 2.5 mg/kg of body weight/day. Every 2 weeks, the dosage was increased by 25 mg/day (by the primary assessor after approval by the second assessor), until a maximum dose of 5 mg/kg of body weight/day was achieved. When both the primary assessor and the patient agreed that there had been marked clinical improvement on 2 consecutive visits, or when the second assessor determined that there were renal function disturbances that did not allow further dosage increases, the CSA dosage was stabilized until the end of the study. In the case of deterioration in renal function, the second investigator recommended either stabilization (for serum creatinine levels between 130% and 150% of the initial value) or reduction (for serum creatinine levels >150% of the initial value) of the CSA dose.

In order to maintain blinding, with each dose modification of active CSA, the same dose modification of placebo CSA was made in the CQ group. If the serum creatinine level did not return to acceptable values (<130% of the initial value) within a period of 4 weeks, the study medication was stopped. During the study, the NSAID dose was kept stable.

**Clinical and laboratory assessments.** All patients were examined by the same primary assessor (RBML) every 2 weeks initially, and every 4 weeks after the CSA dosage had been stabilized.

The following clinical disease variables were assessed: number of swollen joints (among 28 diarthrodial joints); number of tender joints (among 28 joints or groups); duration of morning stiffness; intensity of pain (by 10-cm visual analog scale, with "no pain" and "very severe pain" as extremes); and physician's and patient's global assessment of efficacy, measured at 24 weeks (5-point scale, where 1 = very good effect and 5 = no effect).

An extensive safety and efficacy assessment, including a complete blood cell count, an ESR, and serum levels of liver enzymes, bilirubin, creatinine, potassium, sodium, uric acid, magnesium, and C-reactive protein (CRP), was obtained at study entry and after 12 and 24 weeks of study. A limited assessment, including hemoglobin, white blood cell count, platelet count, serum levels of creatinine, total bilirubin, and potassium, as well as a urinalysis, was obtained at each visit to monitor safety.

**Adverse events.** At each visit, the patient was asked whether side effects had been noticed during the interim. Side effects known to occur frequently during the administration of CSA, such as paraesthesia, hypertrichosis, and tremor, were specifically asked about at 12 and 24 weeks. Clinical safety parameters, determined at each visit, consisted of body weight, blood pressure, and pulse rate.

**Statistics and data analysis.** Based on previous studies of CQ in patients with early RA, we expected at least 40–50% improvement in the swollen joint count in this group after 24 weeks (17). Twenty-two patients per study arm were necessary to provide 90% power to detect a between-group difference in improvement by at least 4 swollen joints. Within-group differences were analyzed by Student's *t*-test for paired data (normally distributed) or Wilcoxon's sign rank test (not normally distributed). Between-group differences were analyzed by Student's *t*-test for unpaired data (normally distributed) or by rank sum test (Mann-Whitney U test) (not normally distributed). Dichotomous variables were analyzed by their proportional group frequencies with Fisher's exact test.

## RESULTS

**Study course data.** Forty-four patients (22 in each group) were included in the study. At study entry, the groups proved to be well balanced with regard to demographic characteristics (Table 1) and disease parameters (Table 2). All patients were taking NSAIDs at the start of the study.

Five patients (11%) did not complete 24 weeks of drug administration. Three of these patients received CQ: one patient withdrew at week 4 because of gastrointestinal (GI) symptoms; the second at week 6 because of the development of rheumatoid vasculitis; the third patient withdrew at week 18 because of a lack of efficacy. The other 2 patients received CSA: one

**Table 1.** Characteristics of study patients, by treatment group

| Characteristic | Cyclosporine (n = 22) | Chloroquine (n = 22) |
|---|---|---|
| Females/males | 13/9 | 14/8 |
| Age | | |
| Mean ± SD | 48 ± 12 | 50 ± 9 |
| Range | 20–68 | 29–65 |
| Disease duration (months) | | |
| Mean ± SD | 7 ± 7 | 6 ± 4 |
| Range | 3–24 | 3–16 |
| Rheumatoid factor positive/negative | 19/3 | 19/3 |
| Erosive/nonerosive disease | 16/6 | 13/9 |

patient withdrew at week 6 because of lack of compliance; the other patient withdrew at week 16 because of a lack of efficacy.

During the study, 8 dosage reductions (25 mg/day) were necessary in 7 patients in the CSA group, and 3 in 3 patients in the CQ group. The CSA dosage was tapered 5 times because of renal function disturbances in 4 of the 7 patients, and 3 times because of other adverse events in the other 3 patients (2 for paresthesia and 1 for headache). All 7 patients were able to continue the study. In the patient receiving CSA who withdrew at week 6 because of rheumatoid vasculitis, the dosage had not been tapered.

The 3 CQ dosage reductions were all required because of GI intolerance during the first 4 weeks of study. One of these patients stopped prematurely because the complaints did not disappear after dosage reduction.

The mean (±SD) CSA dose at the end of the study was 3.6 ± 0.8 mg/kg/day for the 20 patients who completed the study. The mean (±SD) placebo CSA dose in the CQ group at the end of the study was 3.5 ± 0.6 mg/kg/day for the 19 patients who completed the study. The difference of 0.1 mg/kg/day (95% confidence interval [95% CI] −0.1, 0.3 mg/kg/day) was not statistically significant. At the end of the study, all patients were taking 100 mg of active CQ or placebo CQ.

**Efficacy data.** The intention-to-treat analysis, which was not different from the analysis of patients who had completed 24 weeks of treatment, is shown in Table 2. In both groups, all subjective and objective clinical disease parameters improved, and the improvements were similar (not statistically significant). The within-group differences (24 weeks versus study entry) were statistically significant for all clinical disease parameters except for pain in the CQ-treated group.

Global efficacy, as assessed by the patient and the physician (RBML), was similar in both groups (between-group differences not statistically significant). The ESR, CRP level, and hemoglobin concentration did not change significantly in either group.

The values of the clinical disease parameters improved gradually in both treatment groups, occurring mainly between entry and week 12, but still with detectable improvement between weeks 12 and 24. Figure 1 shows, as an example, the course of the swollen joint count in each group. Substantial improvement in the swollen joint count could be detected

**Table 2.** Efficacy of treatment at 24 weeks, compared with baseline, according to clinical and laboratory indicators*

| Parameter | Cyclosporine (n = 22) | | | Chloroquine (n = 22) | | | Difference between treatment groups (95% CI) |
|---|---|---|---|---|---|---|---|
| | At entry | At end | Difference (95% CI) | At entry | At end | Difference (95% CI) | |
| Joint count (28 joints) | | | | | | | |
| Swollen | 16 ± 5 | 9 ± 6 | 7 (4, 10)† | 17 ± 7 | 10 ± 7 | 7 (5, 10)† | 0 (−3, 3) |
| Tender | 14 ± 4 | 9 ± 5 | 5 (3, 7)† | 14 ± 6 | 10 ± 7 | 4 (2, 7)† | 1 (−2, 4) |
| Morning stiffness (minutes) | 62 ± 46 | 28 ± 39 | 34 (17, 51)† | 76 ± 60 | 28 ± 44 | 48 (27, 69)† | −14 (−40, 12) |
| Pain, VAS (cm) | 4.6 ± 2.3 | 3.0 ± 2.5 | 1.6 (0.4, 2.8)† | 4.6 ± 2.1 | 3.7 ± 3.1 | 0.9 (−0.4, 2.2) | 0.7 (−0.9, 2.3) |
| Global assessment (1–5 scale) | | | | | | | |
| Patient | – | 2.6 ± 1.6 | – | – | 2.5 ± 1.2 | – | 0.1 (−0.6, 0.8) |
| Physician | – | 2.3 ± 1.2 | – | – | 2.5 ± 1.1 | – | −0.2 (−0.9, 0.5) |
| ESR (mm/hour) | 40 ± 18 | 43 ± 37 | −3 (−10, 16) | 43 ± 31 | 38 ± 31 | 5 (−2, 12) | −2 (−16, 12) |
| CRP (mg/liter) | 33 ± 28 | 27 ± 39 | 6 (−5, 17) | 37 ± 40 | 33 ± 42 | 4 (−13, 21) | 2 (−18, 22) |
| Hemoglobin (mmoles/liter) | 7.8 ± 0.8 | 7.5 ± 1.1 | 0.3 (−0.1, 0.7) | 7.9 ± 1.0 | 8.0 ± 1.1 | 0.1 (−0.2, 0.4) | 0.2 (−0.3, 0.7) |

* Two patients taking cyclosporine and 3 taking chloroquine did not complete 24 weeks of study (see Results for details); thus, data at study end are the mean ± SD of 20 and 19 patients, respectively. Pain was assessed with a 10-cm visual analog scale (VAS; 0 = no pain; 10 = very severe pain). The patient and the physician used a 5-point scale (1 = very good effect; 5 = no effect) to assess efficacy of treatment. ESR = erythrocyte sedimentation rate (Westergren); CRP = C-reactive protein.
† $P < 0.05$ versus study entry.

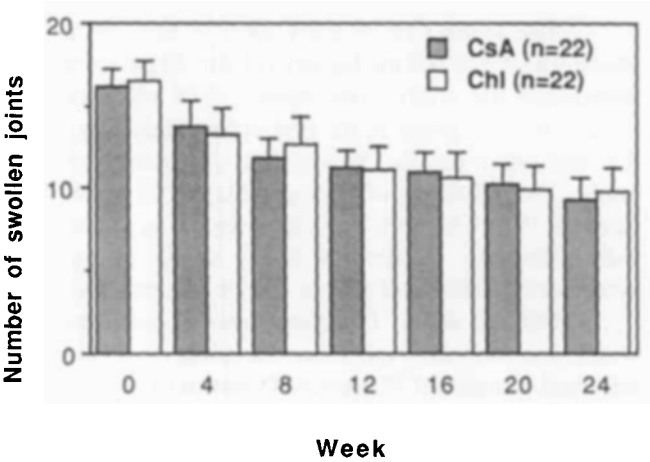


**Figure 1.** Course of swollen joint count (mean and SEM) in 44 patients with early rheumatoid arthritis who were randomly allocated to receive cyclosporine (CsA) or chloroquine (Chl) for 24 weeks.

in both groups between 0 and 4 weeks, suggesting a placebo effect. Between 4 and 24 weeks however, the swollen joint count continuously improved by 4 joints (95% CI 2, 6 joints) in the CSA group and by 3 joints (95% CI 1, 5 joints) in the CQ group. All other clinical disease parameters showed a similar pattern of improvement.

**Disease activity at entry and clinical response.** During the assessment of the data the impression arose that in the CQ group, in contrast to the situation in the CSA group, the patients with mild disease activity particularly benefited from CQ administration. To determine whether good clinical responses to drug administration in both the CSA and the CQ groups could be predicted by disease activity at study entry, a subgroup analysis was performed. One subgroup consisted of patients who had a "good response" (arbitrarily defined as ≥30% improvement in both the swollen joint count and the tender joint count). The other subgroup consisted of all patients who did not fulfill the criteria for "good response" ("nonresponders").

Nine of the 22 CSA patients (41%) and 10 of the 22 CQ patients (45%) experienced a good response (Table 3). In the patients receiving CSA, the values at study entry were similar in the good responders and the nonresponders. In the patients receiving CQ, however, the values at study entry were significantly lower in the good responders than in the nonresponders, indicating that good responders had less severe disease activity at entry than did the nonresponders.

**Toxicity.** The mean systolic blood pressure in the CSA group rose from 131 ± 17 mm Hg (mean ± SD) at study entry to 142 ± 15 mm Hg at study end ($P = 0.01$). In the CQ group, systolic blood pressure remained stable (138 ± 14 mm Hg at entry and 137 ± 14 mm Hg at end; $P$ not significant). The between-group difference in the mean systolic blood pressure at 24 weeks (12 mm Hg; 95% CI 2, 21 mm Hg) was statistically significant ($P < 0.01$). The mean diastolic blood pressure rose from 83 ± 7 mm Hg to 90 ± 9 mm Hg ($P = 0.02$) in the CSA group and from 79 ± 7 to 83 ± 9 ($P = 0.05$) in the CQ group. The between-group difference in the diastolic blood pressure at 24 weeks (3 mm Hg; 95% CI −2, 8 mm Hg) was not statistically significant. Dosage reductions because of high blood pressure in the CSA group were not necessary during the course of the study.

Changes in serum creatinine values in both study groups are shown in Figure 2. In the patients receiving CSA (Figure 2A), a gradual increase in serum creatinine (mean ± SEM entry level 76 ± 18 μmoles/liter, level at 24 weeks 89 ± 31 μmoles/liter, mean increase 13; 95% CI 4, 22) was observed. A plateau phase was reached at week 16, and at 24 weeks, the mean level was 17% above baseline, having become significantly different from baseline at week 6

**Table 3.** Disease activity at study entry predicts the outcome in chloroquine-treated patients, but not in cyclosporine-treated patients*

| | Cyclosporine (n = 22) | | Chloroquine (n = 22) | |
|---|---|---|---|---|
| Parameter | Good response (n = 9) | No response (n = 13) | Good response (n = 10) | No response (n = 12) |
| Swollen joint score | 26 ± 10 | 21 ± 9 | 15 ± 10† | 30 ± 12 |
| Swollen joint count | 17 ± 4 | 15 ± 5 | 13 ± 6‡ | 20 ± 5 |
| Tender joint score | 18 ± 5 | 21 ± 10 | 16 ± 8‡ | 30 ± 15 |
| Tender joint count | 14 ± 4 | 13 ± 5 | 12 ± 5 | 15 ± 8 |
| Pain, VAS (cm) | 4.4 ± 2.1 | 4.7 ± 2.6 | 3.6 ± 1.4§ | 5.4 ± 2.5 |
| ESR (mm/hour) | 43 ± 20 | 38 ± 17 | 25 ± 15‡ | 57 ± 35 |
| CRP (mg/liter) | 31 ± 20 | 34 ± 32 | 14 ± 10‡ | 57 ± 48 |

* A good response was ≥30% improvement (at 24 weeks) in both the swollen joint count and the tender joint count. For the joint scores, each joint was scored for swelling (0 = no swelling, 1 = minimal swelling, 2 = moderate swelling, and 3 = intense swelling) and tenderness to pressure (0 = no pain, 1 = pain, 2 = pain and wincing, and 3 = pain and withdrawal). Values are the mean ± SD. $P$ values were determined by Mann-Whitney U test. VAS = visual analog scale (0–10 cm: 0 = no pain; 10 = very severe pain); ESR = erythrocyte sedimentation rate (Westergren); CRP = C-reactive protein.
† $P < 0.01$ versus no response group.
‡ $P < 0.02$ versus no response group.
§ $P = 0.05$ versus no response group.

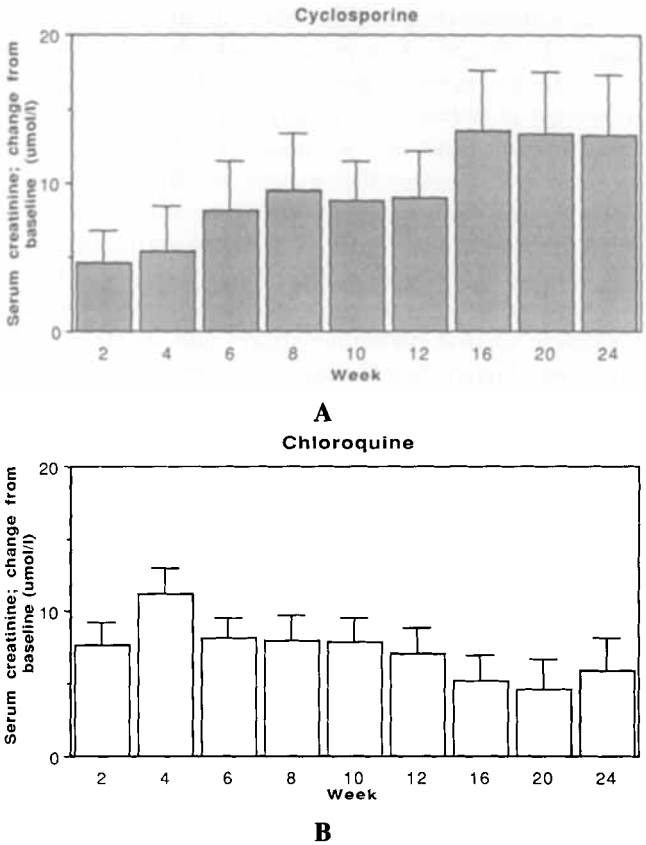


**Figure 2.** Percentage increases in serum creatinine levels (mean and SEM) from baseline levels in 44 patients with early rheumatoid arthritis who received cyclosporine (**A**) or chloroquine (**B**) for 24 weeks.

($P < 0.05$). The increase in serum creatinine was not due to an increase in body weight (entry weight 70 ± 12 kg, weight at 24 weeks 70 ± 12 kg).

The course of serum creatinine changes in the CQ group (Figure 2B) had a skewed parabolic shape, with a maximal increase after 4 weeks of study (+15%) and a decrease during subsequent weeks. The 24-week value was 8% above baseline (entry level 74 ± 8 μmoles/liter, level at week 24 80 ± 12 μmoles/liter, mean increase 6; 95% CI 1, 11). The increase had become statistically significant at week 2 ($P < 0.05$). The increase was not due to an increase in body weight (entry weight 74 ± 14 kg, weight at 24 weeks 74 ± 13 kg).

The increase in the serum creatinine level in the CSA group did not differ significantly from that in the CQ group at any time point. The difference in increase of the serum creatinine between both groups at 24 weeks (7 μmoles/liter; 95% CI −3, 16) was not statistically significant.

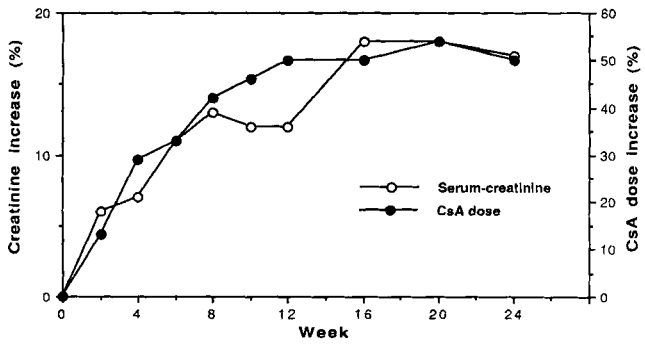


**Figure 3.** Cyclosporine (CsA) dosage compared with serum creatinine increases (mean percentage increase) in 20 patients with early rheumatoid arthritis who had received cyclosporine for 24 weeks.

The course of the rise serum creatinine was related to the course of the increased dose of CSA (Figure 3). The maximum creatinine value as well as the CSA maintenance dose (3.6 mg/kg/day) were both reached after 16 weeks of treatment and remained constant thereafter.

**Adverse events.** The adverse events that occurred during the course of the study are presented in Table 4. GI complaints occurred in 50% of all patients in both groups. These symptoms were mild and temporary in all patients, except 1 patient who was taking CQ. That patient withdrew from the study. Paresthesia (hyperesthesia, crampy sensations, dysesthesia) was common in, and specific for, patients receiving CSA ($P < 0.01$ versus CQ group). Seven patients in the CSA group, compared with 3 patients in the CQ group ($P = 0.11$), had more than a 130% increase in serum creatinine, but the increase was entirely reversible upon reduction of the CSA dosage.

Other adverse events that have been reported

**Table 4.** Adverse events, by treatment group

| Adverse events | Cyclosporine (n = 22) | Chloroquine (n = 22) |
|---|---|---|
| Gastrointestinal complaints | 11 | 11* |
| Paresthesia | 11 | 4 |
| Serum creatinine >130% | 7† | 3 |
| Gingival symptoms | 4 | 0 |
| Hyperkalemia | 4 | 0 |
| Exanthema | 0 | 4 |
| Edema | 3 | 0 |
| Headache | 3 | 2 |
| Hypomagnesemia | 2 | 0 |
| Hypertrichosis | 1 | 1 |
| Tremor | 1 | 0 |
| Liver function abnormalities | 1 | 1 |

* Symptoms led to premature discontinuation in one patient.
† All values normalized after dosage reduction.

to be specific to CSA therapy, such as gingival hyperplasia, hypertrichosis, tremor, hypomagnesemia, and hyperkalemia, occurred preferentially, although not frequently, in the CSA group. Exanthematous eruptions of the skin occurred only in the CQ group. In general, the majority of adverse events were mild and tolerated without the need for dosage reductions.

## DISCUSSION

The main conclusion of the present study is that low-dose CSA is effective and safe in patients with early active RA who require treatment with DMARDs. The safety and efficacy of CSA is comparable to the safety and efficacy of CQ in those patients.

All placebo-controlled and comparative studies in patients with intractable and advanced RA have shown that CSA improves the clinical symptoms of active disease (3–9). The antirheumatic effect of (hydroxy)chloroquine has been established in a large number of placebo-controlled and comparative studies (17–25). In the present study, CSA was equally effective as CQ in alleviating objective and subjective symptoms of active disease in patients with early RA in whom the study medication was their first DMARD. It is not known whether regression-to-the-mean has contributed to the observed effects since a placebo group was not included, for ethical reasons. Regression-to-the-mean will occur particularly during the first weeks of study. The statistically significant improvement between weeks 4 and 24 in both groups suggests that regression-to-the-mean is only partially responsible for the effect measured after 24 weeks. Therefore, the conclusion that CSA (according to our study protocol and with a maintenance dose of 3.6 mg/kg/day), is effective in early RA is justified.

Consistent with reports of studies in RA (3–9) and other autoimmune diseases (26), an effect of CSA on the ESR could not be demonstrated despite clinical efficacy. Nor was a significant effect of CSA on CRP demonstrated in the present study, although, in contrast to the ESR, a tendency toward a decrease was noted. A decrease in CRP has previously been found in patients with advanced RA (5,6,9), and lack of statistical power might be the reason for not detecting such a difference in the present study.

CSA primarily interferes with the function of activated T cells, while CQ is thought to mainly inhibit monocyte function (27). Recently, we have demonstrated that CQ can also inhibit the function of activated T cells (28). Therefore, comparable clinical efficacy of both drugs might reflect comparable inhibition of T cell activation in patients with early RA.

In the present study, it was found that CSA treatment of patients with early RA did not seriously impair renal function, as measured by the serum creatinine. The maintenance dose of CSA (3.6 mg/kg/day) was similar to the maintenance dose that had been reached in one study of patients with advanced RA (3.8 mg/kg/day), using the same approach of CSA dose-titration (7). However, the 27% increase in serum creatinine in that particular study, and in others (3–9,13), was higher than the increase seen in the present study (17%). This discrepancy might be explained by the substantially shorter disease duration in patients in the present study than in patients in the previous studies. Further, the mild impairment of renal function in the patients receiving CSA should be seen in light of that occurring in the control group. An unexpected rise in serum creatinine was demonstrated in the patients who received CQ, a phenomenon that has been described only in a case report (29). The shape of the serum creatinine curve, with a maximum at the moment of maximal CQ dose (week 4) and a statistically significant increase after only 2 weeks of treatment (4 weeks earlier than in the patients receiving CSA), highly suggests a correlation between CQ administration and impairment of renal function.

Adverse events, other than renal toxicity, occurred frequently in both groups, especially GI complaints. These adverse events, however, were manageable and temporary. All patients, except 1 patient receiving CQ, were able to continue the study. In contrast, premature discontinuation due to adverse events has been reported in 6% (7), 20% (8), and 15% (9) of patients with advanced RA who were being treated with low-dose CSA. The rate of premature discontinuation due to adverse events was 17% among 283 patients with intractable and advanced RA treated with high- or low-dose CSA (30). The low frequency of "CSA-specific" adverse events, except for mild paresthesia, and the absence of premature discontinuation due to adverse events, support the hypothesis that patients with early RA can tolerate CSA better than patients with advanced disease.

In summary, it can be concluded that CSA at a maintenance dose of 3.6 mg/kg/day is equally effective as CQ in alleviating the signs and symptoms of early active RA. In contrast to the situation in patients with advanced RA, however, CSA administration under the precautions described in the present study resulted in only slightly impaired renal function. Careful followup

of the serum creatinine concentration brought to light an unexpected finding of renal function impairment in the CQ group. The results of this pilot study should open the doors to long-term followup of patients with CSA-treated early RA, in order to establish the real value of CSA in the retardation of radiologic progression and long-term preservation of functional capacity.

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