

Combination Treatment With Methotrexate, Cyclosporine, and Intraarticular Betamethasone Compared With Methotrexate and Intraarticular Betamethasone in Early Active Rheumatoid Arthritis

An Investigator-Initiated, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study

Merete Lund Hetland,¹ Kristian Stengaard-Pedersen,² Peter Junker,³ Tine Lottenburger,⁴ Torkell Ellingsen,² Lis Smedegaard Andersen,⁴ Ib Hansen,² Henrik Skjødt,¹ Jens Kristian Pedersen,⁴ Ulrik Birk Lauridsen,¹ Anders Svendsen,⁴ Ulrik Tarp,² Jan Pødenphant,⁵ Gert Hansen,⁴ Hanne Lindegaard,³ Anselmo de Carvalho,² Mikkel Østergaard,⁴ Kim Hørslev-Petersen,⁴ and the CIMESTRA Study Group

Objective. To investigate whether disease control can be achieved in early active rheumatoid arthritis (RA) by treatment with methotrexate and intraarticular betamethasone, and whether the addition of cyclosporine to the regimen has any additional effect.

Methods. Patients (n = 160) were randomized to

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¹Merete Lund Hetland, MD, PhD, Henrik Skjødt, MD, PhD, Ulrik Birk Lauridsen, MD: Copenhagen University Hospital, Hvidovre, Denmark; ²Kristian Stengaard-Pedersen, MD, DMSc, Torkell Ellingsen, MD, PhD, Ib Hansen, MD, Ulrik Tarp, MD, DMSc, Anselmo de Carvalho, MD: Århus University Hospital, Århus, Denmark; ³Peter Junker, MD, DMSc, Hanne Lindegaard, MD, PhD: Odense University Hospital, Odense, Denmark; ⁴Tine Lottenburger, MD, Lis Smedegaard Andersen, MD, PhD, Jens Kristian Pedersen, MD, Anders Svendsen, MD, PhD, Gert Hansen, MD, Mikkel Østergaard, MD, PhD, DMSc, Kim Hørslev-Petersen, MD, DMSc: Rheumatism Hospital, University of Southern Denmark, Grasten, Denmark; ⁵Jan Pødenphant, MD, DMSc: Copenhagen University Hospital, Herlev, Denmark.

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Address correspondence and reprint requests to Kim Hørslev-Petersen, MD, DSc, Rheumatism Hospital, University of Southern Denmark, Toldbodgade 3, DK-6300 Grasten, Denmark. E-mail: khorslevpetersen@gigtforeningen.dk.

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receive methotrexate 7.5 mg/week plus cyclosporine 2.5 mg/kg of body weight/day (combination therapy) or methotrexate plus placebo-cyclosporine (monotherapy). At weeks 0, 2, 4, 6, and 8 and every 4 weeks thereafter, betamethasone was injected into swollen joints (maximum 4 joints or 4 ml per visit). Beginning at week 8, if synovitis was present, the methotrexate dosage was increased stepwise up to 20 mg/week, with a subsequent stepwise increase in the cyclosporine or placebo-cyclosporine dosage up to 4 mg/kg.

Results. At 52 weeks, 20% improvement according to the American College of Rheumatology criteria (ACR20) was achieved in 85% of the combination therapy group versus 68% of the monotherapy group ($P = 0.02$). The median individual overall ACR response (ACR-N) in the 2 groups was 80.0% (interquartile range 40.1–91.8%) and 54.5% (interquartile range 2.4–87.8%), respectively ($P = 0.025$). At 48 and 52 weeks, ACR remission criteria were met in 35% of the combination therapy group and 28% of the monotherapy group. Progression in the Larsen score at 52 weeks was -0.2 ± 6.5 and 0.4 ± 6.9 (mean \pm SD) in the combination therapy and monotherapy groups, respectively. Serum creatinine levels increased by 7%, and hypertrichosis was more prevalent, in the combination therapy group.

Conclusion. Combined treatment with methotrexate and intraarticular glucocorticoid showed excellent

disease control and stopped the progression of erosions in patients with early active RA, who had a poor prognosis. Addition of cyclosporine improved the ACR20 and ACR-N responses, whereas the ACR50 and ACR70 responses, remission rates, and radiographic changes did not differ between the 2 study groups.

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with rapid loss of physical function (1), and erosive changes often occur during the first years (2). Early treatment with disease-modifying antirheumatic drugs (DMARDs) improves the long-term outcome (3), and this is reflected in the American College of Rheumatology (ACR) guidelines for RA treatment (4). The optimum treatment strategy for early RA has not yet been established, and such issues as initial monotherapy versus combination therapy (3,5) and the role of glucocorticoids (6,7) are still in dispute.

Cyclosporine has been demonstrated to reduce the progression of erosions in RA and has been used successfully in combination with methotrexate (8,9). Cyclosporine acts via T lymphocytes, which are considered to be central in the pathogenesis of early RA (10). Concern about renal side effects, however, has limited its use, although with low-dose regimens, side effects are few (11).

DMARDs have a delayed onset of action, whereas glucocorticoids relieve signs and symptoms within days, appear to have some disease-modifying potential (6), and are used as bridging therapy (4). Intraarticular administration of glucocorticoids may be used to obtain rapid control of disease with minimum toxicity (7).

The aims of the Cyclosporine, Methotrexate, Steroid in RA (CIMESTRA) trial were to investigate whether disease control could be achieved and maintained in early RA by immediate and intensive treatment with methotrexate and intraarticular betamethasone, and whether combining this therapy with cyclosporine had any additional clinical effect or steroid-sparing potential. The primary end point was the proportion of patients who achieved 20% improvement according to the ACR criteria (ACR20) (12). Among the secondary end points were clinical remission, the cumulative dose of betamethasone, ACR50 and ACR70 responses, and radiographic outcome.

PATIENTS AND METHODS

Role of the funding source. Novartis Healthcare A/S (Copenhagen, Denmark) kindly provided the cyclosporine (Sandimmune Neoral) and the placebo-cyclosporine and spon-

sored an independent good clinical practice monitor. Nycomed (Roskilde, Denmark) provided the methotrexate (Emthexate), folic acid (Apovit), and calcium carbonate/vitamin D₃ (CaviD). Schering-Plough A/S (Farum, Denmark) provided the injectable betamethasone (Diprosan), and Merck, Sharp, & Dohme (Glostrup, Denmark) provided the alendronate (Fosamax). The study sponsors were not involved in the study set-up, data collection, or the analysis and interpretation of the data, and had no influence on the publishing of the data.

Study design. The CIMESTRA study was an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial that included 160 consecutive patients with early active RA. Patients from 5 rheumatology centers in Denmark were entered into the study from October 1999 to October 2002 (11–64 patients per center).

Inclusion and exclusion criteria. Inclusion criteria were fulfillment of the ACR (formerly, the American Rheumatism Association) 1987 revised criteria for RA (13), active disease of <6 months' duration, at least 2 swollen joints at baseline, and age between 18 and 75 years. Exclusion criteria were treatment with glucocorticoids in the preceding 4 weeks, previous use of DMARDs, past or present malignancy, a diastolic blood pressure of >90 mm Hg despite treatment with antihypertensive agents, a serum concentration of creatinine above the upper normal limit, infection with either parvovirus B19, hepatitis B, hepatitis C, or human immunodeficiency virus, and any condition contraindicated for the study medication.

Treatment strategy. The CIMESTRA trial consisted of 2 treatment arms: one consisted of methotrexate 7.5 mg/week plus cyclosporine 2.5 mg/kg of body weight/day (combination therapy group), and the other consisted of methotrexate 7.5 mg/week plus placebo-cyclosporine (monotherapy group). At weeks 0, 2, 4, 6, and 8 and every 4 weeks thereafter up to week 52, the patients were given intraarticular injections of betamethasone (7 mg/ml) in all swollen joints (maximum 4 joints or 4 ml per visit). Oral glucocorticoids were not allowed. Beginning at week 8, if swollen joints were present, the methotrexate dosage was increased by 2.5 mg/week every 4 weeks up to a maximum of 20 mg/week, and beginning at week 28, the cyclosporine/placebo-cyclosporine dosage was increased stepwise by 0.5 mg/day every 4 weeks to a maximum of 4 mg/kg of body weight. Joints were evaluated and injections were given by an independent, blinded, and trained assessor. All authors except AdC were assessors for one or more patients.

All patients received folic acid as well as calcium and vitamin D supplementation. Dual x-ray absorptiometry of the femoral neck and lumbar spine was performed at the start of the study, and patients with a Z score of <0 in the femoral neck or lumbar spine received alendronate 10 mg/day. Mild analgesics were given on demand.

Randomization. Patients were randomized in blocks of 4 from a computer-generated list of study numbers. The code was kept locked up, and the study numbers were assigned centrally by the good clinical practice monitor.

Outcome measures. The primary efficacy end point was the ACR20 response at week 52. Secondary end points included remission, cumulative dose of betamethasone, ACR50 response, and ACR70 response at week 52. Remission was defined according to the ACR criteria for remission in RA (14) and must have been present at both 48 weeks and 52

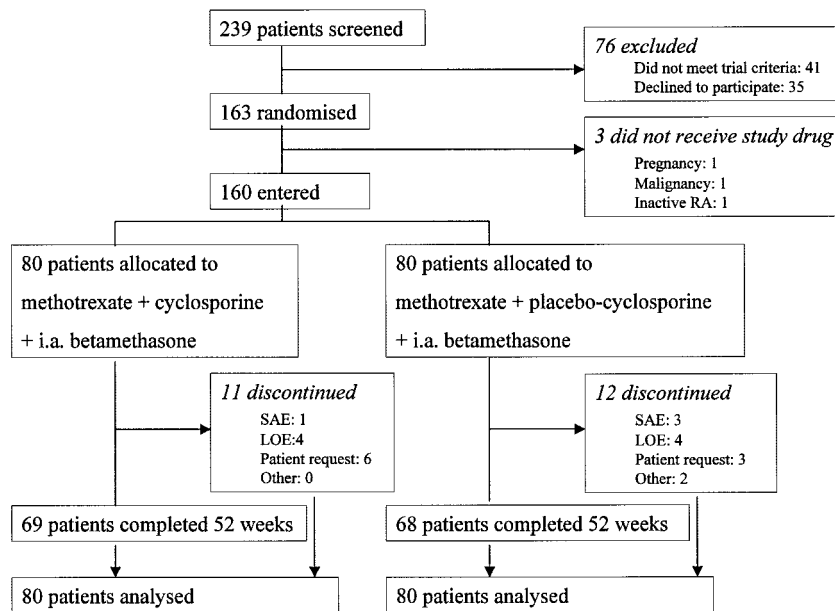


Figure 1. Flow chart showing the distribution of the study patients from initial contact to completion of the study. RA = rheumatoid arthritis; i.a. = intraarticular; SAE = serious adverse event; LOE = lack of efficacy.

weeks to be acknowledged. Remission was also defined according to the Disease Activity Score in 28 joints (DAS28; scores <2.6) (15) (available online at <http://www.das-score.nl>). The individual overall ACR response (ACR-N) at week 52, and the cumulative response over time (the area under the curve) for the ACR-N in the 2 treatment groups were also calculated. These latter 3 assessments were added because of their recent use in other reported studies (16,17). Disability was assessed with the Health Assessment Questionnaire (HAQ) at each visit (12).

Radiographs of the hands (posteroanterior and Nørgaard [18] projections), wrists (posteroanterior and lateral projections), and forefeet (anteroposterior view) were obtained at baseline and at weeks 24 and 52. The radiographs were evaluated by an independent senior musculoskeletal radiologist (AdC), who had performed Larsen scoring in several previous studies and who was blinded to the chronological sequence and the treatment assigned (19). The proximal interphalangeal and the first interphalangeal joints of the fingers, the metacarpophalangeal joints, the metatarsophalangeal joints, and the wrist joints were given a score from 0 to 5 according to the Larsen method (20). A score of 1 (i.e., nonerosive changes: joint space narrowing, soft tissue swelling, and juxtaarticular halisteresis) was omitted. The radiographic joint damage, or Larsen, score (range 0–200) was calculated by summing all scores (the wrist scores were weighted by multiplying by a factor 5). The primary radiographic end point was change in the Larsen score from baseline. The estimated yearly rate of progression in the Larsen score was calculated according to the duration of disease and the baseline Larsen score for each patient (17).

Treatment adjustment for adverse events. The dosage of cyclosporine/placebo-cyclosporine was reduced if the serum

creatinine level increased by >30% compared with the baseline level. In the case of a persistent increase, cyclosporine/placebo-cyclosporine was withdrawn. Patients who developed hypertension (blood pressure >140/90 mm Hg) were treated with amlodipine 5–10 mg/day, and the cyclosporine/placebo-cyclosporine dosage was reduced until the blood pressure was normalized. If hypertension persisted, cyclosporine/placebo-cyclosporine was discontinued. Side effects of methotrexate were handled in accordance with local guidelines. In the case of severe toxicity, the patient was excluded from the study, and the study medication was withdrawn.

Ethical considerations. All patients gave their written informed consent. The protocol was approved by the national health authorities and ethics committees in all 5 participating counties. The trial was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation 1996 revised Guidelines for Good Clinical Practice in the European Community.

Statistical analysis. Eighty patients in each study arm, with an expected dropout rate of 10%, gave 80% power to detect a 20% difference in the response rate between the 2 arms at $\alpha = 0.05$ (2-sided test). This was calculated on an expected response rate of 70% in the monotherapy group (21).

Comparisons between groups were made with Fisher's exact test for dichotomous responses and the Mann-Whitney U test for nondichotomous responses. Changes over time were analyzed with McNemar's test for dichotomous responses and Wilcoxon's signed rank sum test for nondichotomous responses. To adjust for possible demographic and baseline confounders, a logistic regression analysis was used to compare the odds of an ACR20 response at 1 year. Age, sex, rheumatoid factor positivity, and anti-cyclic citrullinated peptide (anti-

Table 1. Baseline demographic, clinical, and laboratory characteristics of the patients with early, active rheumatoid arthritis, by treatment group*

	Methotrexate plus cyclosporine (n = 80)	Methotrexate plus placebo-cyclosporine (n = 80)
Age, median (IQR) years	53.2 (44.5–62.4)	51.0 (39.5–62.5)
Female, %	64	70
Disease duration, median (IQR) months	3.2 (2.4–4.6)	3.9 (2.8–4.6)
Rheumatoid factor positive, %	70	59
Anti-CCP positive, %	72†	45
No. of tender joints, median (IQR) (range 0–40)	14 (7–20)	14 (8–20)
No. of swollen joints, median (IQR) (range 0–40)	12 (6–14)	11 (6–15)
Physician's global assessment, median (IQR) (0–100-mm VAS)	54 (37–65)	61 (39–71)
Patient's assessment of pain, median (IQR) (0–100-mm VAS)	46 (28–70)	48 (29–65)
Patient's global assessment, median (IQR) (0–100-mm VAS)	50 (28–70)	52 (32–73)
Serum CRP, median (IQR) mg/liter	21 (10–42)	19 (8–46)
ESR, median (IQR) mm/hour	28 (10–48)	27 (10–47)
DAS28 score, mean ± SD	5.31 ± 1.34	5.51 ± 1.27
HAQ score, median (IQR) (range 0–3)	1.0 (0.4–1.5)	0.9 (0.5–1.4)
Blood pressure, median (IQR) mm Hg	130/80 (120–140/78–88)	130/80 (120–139/72–85)
Serum creatinine, mean ± SD μmoles/liter	75.4 ± 11.0	75.3 ± 12.2
NSAID use, %	60	66
Alendronate use, %	40	40
Erosive disease, %	46	49
Larsen score		
Median (IQR)	0 (0–10)	0 (0–6)
Mean ± SD	6.0 ± 10.1	4.6 ± 7.4
Estimated yearly rate of progression, mean ± SD	25.0 ± 41.3	14.6 ± 24.4

* IQR = interquartile range; anti-CCP = anti-cyclic citrullinated peptide antibodies (in serum); VAS = visual analog scale; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; NSAID = nonsteroidal antiinflammatory drug.

† $P < 0.001$ by chi-square test. The remaining baseline characteristics were not statistically significantly different between treatment groups.

CCP) antibody positivity at baseline were included in the model. Possible interactions between the treatment group and age, sex, rheumatoid factor positivity, and anti-CCP positivity were also analyzed. Results of the unadjusted models are presented because the results of the adjusted and unadjusted models were in agreement. Data are reported as the mean ± SD for variables in which normal distribution was found; otherwise, the data are reported as the median (interquartile range [IQR]).

Analysis was by intent-to-treat. We used the last observation carried forward approach for missing data. Intent-to-treat analysis without the last observation carried forward and the completers' analysis were also performed and gave similar results (data not shown).

The R software package (22) was used for the statistical analysis, which was performed by 2 independent statisticians.

RESULTS

Patient characteristics. Eighty patients received combination therapy (methotrexate and cyclosporine), and 80 patients received monotherapy (methotrexate and placebo-cyclosporine) (Figure 1). At each visit, betamethasone was injected into swollen joints. Baseline characteristics of the 2 treatment groups did not differ

significantly, except for serum anti-CCP antibodies, which were more prevalent in the combination therapy group (Table 1). A total of 137 patients (86%) completed the study. Reasons for withdrawal from the study are shown in Figure 1.

The median dosage of methotrexate at 52 weeks was 12.5 mg/week (IQR 10.0–18.1) in the combination therapy group versus 15 mg/week (IQR 11.9–18.1) in the monotherapy group ($P = 0.17$). The cyclosporine/placebo-cyclosporine dosage was increased in 10% of the combination therapy group and 19% of the monotherapy group. The cumulative dose of betamethasone from week 12 onward was higher in the monotherapy group (median 5.8 ml [IQR 2.5–11.1 ml]) than in the combination therapy group (3.3 ml [IQR 1.0–9.1 ml]) ($P = 0.03$). In the first 12 weeks, there was no difference in the cumulative dose of betamethasone between the 2 groups: 6.3 ml (IQR 4.0–8.5 ml) in the monotherapy group versus 5.5 ml (IQR 4.0–8.0 ml) in the combination therapy group ($P = 0.47$).

Radiographs were obtained at baseline and at 52 weeks in 157 patients (79 receiving monotherapy and 78

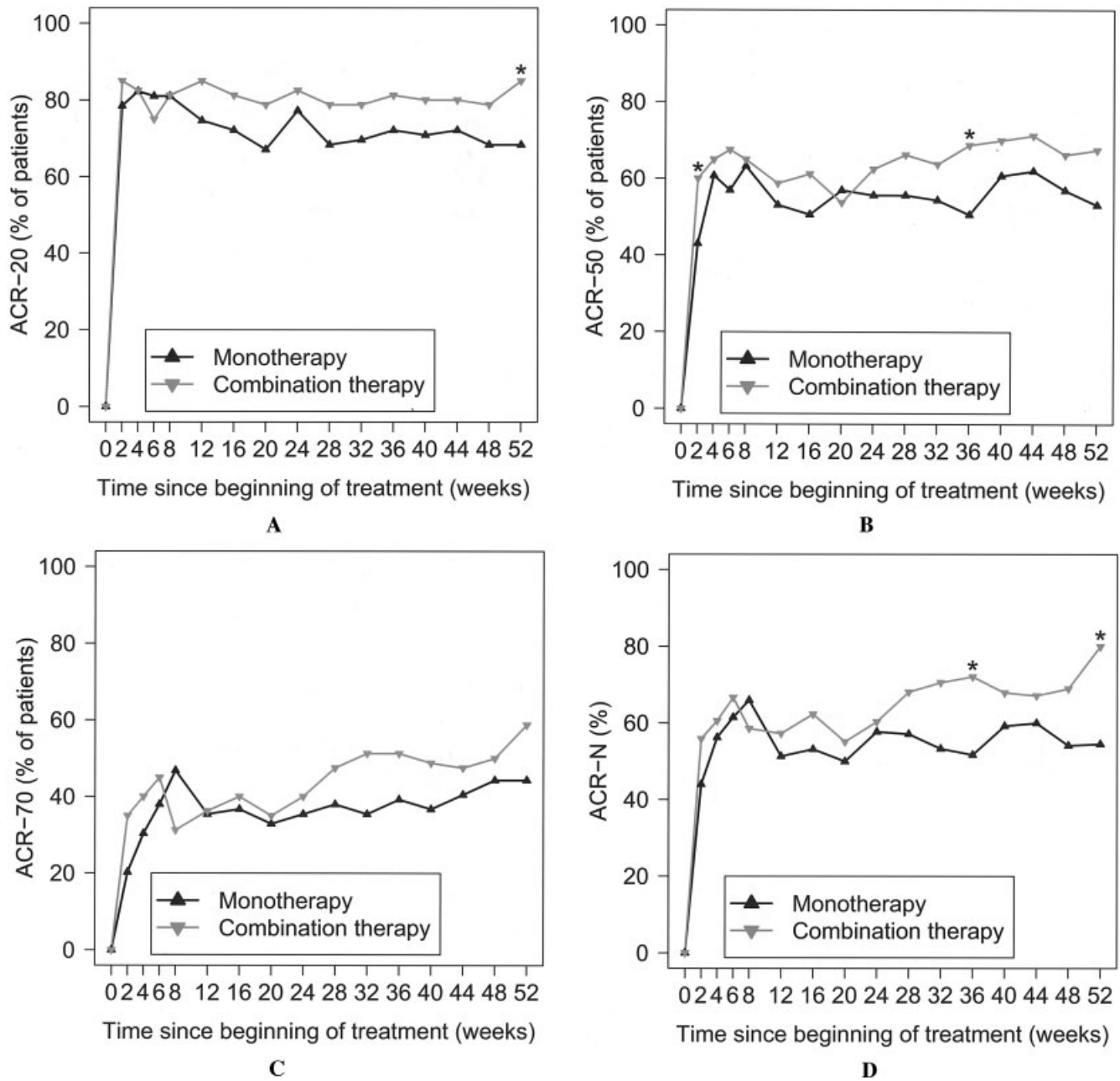


Figure 2. Proportion of patients in each treatment group who achieved responses at each study visit relative to baseline, according to the American College of Rheumatology (ACR) improvement criteria. **A**, ACR 20% response. **B**, ACR 50% response. **C**, ACR 70% response. **D**, Individual overall ACR response (ACR-N) at 52 weeks. * = $P < 0.05$ for difference between the 2 treatment groups, by Fisher's exact test (**A-C**) or by Mann-Whitney U test (**D**).

receiving combination therapy). At baseline, the percentages of patients with erosions, the Larsen scores, and the estimated yearly rates of progression in the Larsen score were not significantly different between the 2 groups (Table 1).

Clinical efficacy. The proportion of patients achieving an ACR20 response at 52 weeks was higher in the combination therapy group (85% of patients) than in the monotherapy group (68%) (Figure 2A), yielding an odds ratio of 2.61 (95% confidence interval 1.14–6.25;

$P = 0.02$). Similarly, the proportions of patients achieving ACR50 and ACR70 responses were consistently higher for the combination therapy group than for the monotherapy group, although these differences did not reach statistical significance (Figure 2B and C). The ACR-N response at 52 weeks was higher in the combination therapy group than in the monotherapy group (median 80.0% [IQR 40.1–91.8] versus 54.5% [IQR 2.4–87.8]; $P = 0.03$) (Figure 2D). The areas under the curve for the ACR-N response from week 12 to week 52 were greater for the patients in the combination therapy group than for the patients in the monotherapy group (64.8% [IQR 35.5–80.0] versus 48.7% [IQR 13.2–74.1]; $P = 0.045$).

The proportion of patients achieving ACR remission at both 48 and 52 weeks (including the absence of glucocorticoid injections after week 44) in the combination therapy and monotherapy groups was 35% and 28%, respectively ($P = 0.39$). The proportion of patients achieving remission according to the DAS28 score at both 48 and 52 weeks in the combination therapy and monotherapy groups was 43% and 34%, respectively ($P = 0.33$). There was a sustained reduction in median HAQ scores to 0.3 (IQR 0–0.8) and 0.4 (IQR 0–0.9) at visit 1 in the combination therapy and monotherapy groups ($P < 0.001$ versus baseline; P not significant between treatment groups). At 52 weeks, 62 patients in the combination therapy group and 54 patients in the monotherapy group had no swollen joints ($P = 0.22$ for between-group comparison), 47 and 35 had HAQ scores of ≤ 0.25 ($P = 0.08$), and 37 and 35 had pain scores of ≤ 10 mm on a 100-mm visual analog scale ($P = 0.87$).

Radiographic evaluation of joint damage. The estimated yearly rate of progression in the Larsen score was 25.0 ± 41.3 (mean \pm SD) in the combination therapy group and 14.6 ± 24.4 in the monotherapy group (Table 1). The observed rates of progression in the Larsen score at 24 and 52 weeks were -0.7 ± 5.0 and -0.2 ± 6.5 in the combination therapy group and -1.2 ± 5.5 and 0.4 ± 6.9 in the monotherapy group, respectively (P not significant for comparisons over time or between treatment groups) (Figure 3). At baseline, 48% of the patients had bone erosions noted on radiographs, whereas the corresponding values at 24 and 52 weeks were 39% and 44%. There was no difference in radiographic evidence of the development of bone erosions in patients who were and those who were not taking alendronate.

Adverse events. Median increases in the serum creatinine level at 52 weeks were 7% (range –21 to 78)

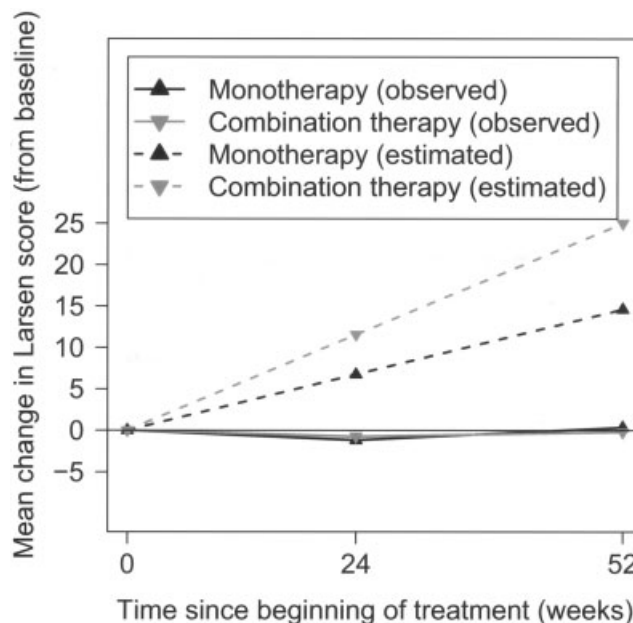


Figure 3. Estimated and observed radiographic changes in the 2 treatment groups at 24 and 52 weeks of study, based on the mean change in Larsen scores relative to baseline.

and 2% (range –23 to 47) in the combination therapy and monotherapy groups ($P < 0.001$ for between-group comparison). Serum creatinine levels increased more than 30% over baseline levels in 15 patients in the combination therapy group and 5 patients in the monotherapy group (range 30–78% and 30–92%, respectively) (Table 2). In 4 of these patients (all receiving combination therapy), cyclosporine was withdrawn because of persistently high serum creatinine levels (a 37–62% increase), after which, the serum creatinine levels decreased to normal.

At 52 weeks, antihypertensive treatment had been added to the combination therapy in 17 patients and to the monotherapy in 9 patients to keep their blood pressure below 140/90 mm Hg (Table 2). Three patients receiving combination therapy and 1 receiving monotherapy had a blood pressure of more than 145/95 mm Hg at 2 consecutive visits. One patient discontinued cyclosporine because of persistent hypertension. Five patients receiving combination therapy and 4 receiving monotherapy discontinued cyclosporine/placebo-cyclosporine because of other side effects. Hypertrichosis was 4 times more prevalent in the cyclosporine-treated patients.

Serious adverse events leading to study withdrawal were seen in 3 patients receiving monotherapy

Table 2. Adverse events*

Type of adverse event	Methotrexate plus cyclosporine (n = 80)	Methotrexate plus placebo-cyclosporine (n = 80)	P
Dyspepsia	18 (23)	16 (20)	0.85
Hypertrichosis	26 (33)	6 (8)	<0.001
Constipation	3 (4)	9 (11)	0.13
Insomnia	4 (5)	9 (11)	0.25
Antihypertensive agent added due to hypertension (BP >140/90 mm Hg)	17 (21)	9 (11)	0.13
>10% decrease in serum albumin versus baseline	6 (8)	9 (11)	0.59
>30% increase in serum creatinine versus baseline	15 (19)	5 (6)	0.03

* Shown are the number (%) of adverse events that occurred in >10% of patients in either treatment group. *P* values were determined by Fisher's exact test. BP = blood pressure.

(thrombocytopenia, leukopenia, and severely elevated liver enzyme levels) and in 1 patient receiving combination therapy (breast cancer). No deaths occurred. Infections requiring hospitalization occurred in 2 patients receiving combination therapy and 2 receiving monotherapy. Three patients (2 in the combination therapy group and 1 in the monotherapy group) were admitted to the hospital because of cardiologic symptoms, which were considered to be unrelated to the study therapy. Basocellular carcinoma was diagnosed in 1 patient (monotherapy group).

DISCUSSION

Our main finding was that aggressive step-up treatment with methotrexate and intraarticular betamethasone produced rapid and effective disease control in patients with early active RA. Addition of cyclosporine further improved the ACR20 and ACR-N, but not the ACR50 and ACR70, response rates and reduced the need for intraarticular glucocorticoids. Neither treatment arm showed radiographic progression of erosions. Mild side effects and high adherence to treatment added further benefit to the strategy.

Previous studies have shown the importance of early intervention in RA (5,16,21,23). In the CIMESTRA trial, treatment was initiated within the first 6 months of disease onset. The strategy was to suppress signs of disease activity by aggressive treatment with intraarticular betamethasone and traditional DMARDs. Unlike findings in most other studies of patients with early RA treated with nonbiologic agents (5,7,23), the clinical benefit from the treatment regimens was reflected in a rapid and sustained decline in all core parameters of disease activity after 2 weeks. Furthermore, despite a high prevalence of risk factors for progressive disease, about one-third of the patients

achieved remission according to the ACR criteria at both weeks 48 and 52, and ~60% achieved an ACR50 response at 52 weeks. These clinical responses are of the same order of magnitude as those reported in trials of tumor necrosis factor α (TNF α) inhibitors (17,24).

We chose methotrexate as first-line therapy because of its proven effectiveness and acceptable toxicity (4,25,26) and in accordance with international treatment guidelines. Additional cyclosporine increases the clinical efficacy (8,9) and may beneficially alter the pharmacokinetics of methotrexate (27). The tardive effect of combination therapy on the ACR-N response and on glucocorticoid use seen from week 12 and onward supported a disease-modifying effect of cyclosporine. However, the difference in the amount of glucocorticoid used in the 2 treatment arms makes it difficult to properly evaluate the effects of cyclosporine. More glucocorticoid was used in the monotherapy group, which may have influenced the clinical response and, possibly, the radiographic changes. The risk of underestimating a potential benefit of cyclosporine was enhanced by the skewed distribution of anti-CCP antibodies, with more positive patients in the monotherapy group predicting a higher risk of a more severe disease course in this group than in the combination therapy group.

Consistent with a previous study of combined cyclosporine and methotrexate in early RA (7), we used a low dose of cyclosporine. However, in contrast to that study, we primarily increased the methotrexate dosage rather than the cyclosporine dosage. This strategy was effective and safe.

Glucocorticoids rapidly relieve signs and symptoms of RA, but they also reduce joint destruction (6,28). Intraarticular administration, which ensures a high concentration of glucocorticoids at the site of

inflammation and reduces synovitis more than methotrexate alone, has been used successfully in previous studies of early RA (7,16,28). In the CIMESTRA study, betamethasone was effective as bridging therapy, and the cumulative dose was moderate. The intraarticular injections had a rapid onset of antiinflammatory action, and the need for additional injections was low. On the assumption that 3 mg of betamethasone is equivalent to 20 mg of prednisolone, the median dose applied corresponded to <2 mg of prednisolone/day (29). The addition of cyclosporine to methotrexate reduced the amount of betamethasone that was necessary to control disease activity.

In general, studies of early RA have showed radiographic progression during the first year despite combination therapy (5–7,21,23,30,31). In the present study, no change in the radiographic joint damage score was observed, despite a high baseline prevalence of risk factors for radiographic progression. This result, which was achieved with traditional DMARDs and intraarticular betamethasone, was similar to that achieved with TNF α inhibitors (17,24). The findings are strengthened by the fact that nonerosive changes were omitted in the calculation of the Larsen score, so the radiographic scoring included only definite erosive changes. We sought to achieve a high-quality radiographic evaluation by having a senior musculoskeletal radiologist with many years of experience in Larsen scoring interpret the radiographs (19). Radiographs were evaluated without knowledge of the chronological sequence or the treatment assignment. Since the radiographic scores were almost identical in the 2 groups, it is unlikely that other radiographic scoring methods, such as the Sharp/van der Heijde method, would have demonstrated statistically significant differences between the treatment arms.

With a treatment strategy similar to that used in previous studies (11), we minimized side effects of cyclosporine by using a low-dose treatment regimen with standard monitoring of renal function and blood pressure. The most common side effect was moderate hypertrichosis, which in no case necessitated withdrawal of therapy.

Early RA requires close monitoring and intensive treatment. The importance of frequent medical visits was demonstrated in a recent study (16). In the present study, patients were seen once every 2 weeks during the first 2 months and once a month thereafter, which may have contributed to the excellent response to treatment. The inclusion of a control group that did not receive glucocorticoid injections would have provided interesting additional information about the clinical and radio-

graphic impact of intraarticular glucocorticoid injections.

In conclusion, early aggressive intervention with methotrexate and intraarticular glucocorticoids, with or without cyclosporine, provided safe and sustained relief of signs and symptoms of synovitis and stopped radiographic progression of RA. Addition of cyclosporine to the methotrexate therapy improved the ACR20 and ACR-N responses, but did not influence the ACR50 and ACR70 responses, remission rates, or radiographic changes. The role of cyclosporine in the treatment of early RA remains to be investigated further, particularly with regard to the effectiveness/toxicity index and long-term radiographic outcome.

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APPENDIX A: THE CIMESTRA STUDY GROUP

Members of the CIMESTRA Study Group are as follows.

Investigators: Drs. T. Lorenzen and S. H. Jensen, Gråsten Rheumatism Hospital (Grasten, Denmark); Drs. H. Bendtsen, K. L. Faarvang, M. S. Hansen, T. M. Hansen, and H. Nielsen, Herlev Hospital (Herlev, Denmark); Drs. S. Jacobsen and O. Majgaard, Hvidovre Hospital (Hvidovre, Denmark); and Drs. J. Beier, L. Ejstrup, J. B. Knudsen, and H. Laustrop, Odense Hospital (Odense, Denmark).

Statisticians: K. Larsen, Hvidovre Hospital, and N. S. Krogh, Zitelab ApS (Frederiksberg, Denmark).

Imaging group: J. Vallø, Gråsten Rheumatism Hospital, H. S. Thomsen, Herlev Hospital, B. Ejbjerg, Hvidovre Hospital, T. Torfing, Odense Hospital, and A. G. Jurik, Århus Hospital (Århus, Denmark).

Study nurses: G. Bukh, Herlev Hospital, J. Frederiksen, Gråsten Rheumatism Hospital, L. Gerdes, Århus Hospital, H. Holm, Odense Hospital, K. B. Lorentzen, Odense Hospital, B. Z. Pedersen, Hvidovre Hospital, P. Rasmussen, Gråsten Rheumatism Hospital, and K. Theilgård, Gråsten Rheumatism Hospital.