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Retardation of Joint Damage in Patients With Early Rheumatoid Arthritis by Initial Aggressive Treatment With Disease-Modifying Antirheumatic Drugs

Five-Year Experience From the FIN-RACo Study

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Objective. **To evaluate the long-term frequency of disease remissions and the progression of joint damage in patients with early rheumatoid arthritis (RA) who were initially randomized to 2 years of treatment with either a combination of 3 disease-modifying antirheumatic drugs (DMARDs) or a single DMARD.**

Methods. **In this multicenter prospective followup study, a cohort of 195 patients with early, clinically active RA was randomly assigned to treatment with a combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone or with a single DMARD (initially, sulfasalazine) with or without prednisolone. After 2 years, the DMARD and prednisolone treatments became unrestricted, but were still targeted toward remission. The long-term effectiveness was assessed by recording the frequency of remissions and the extent of joint damage seen on radiographs of the hands and feet obtained annually up to 5 years. Radiographs were assessed by the Larsen score.**

Results. **A total of 160 patients (78 in the combination group and 82 in the single group) completed the 5-year extension study. At 2 years, 40% of the patients in the combination-DMARD group and 18% in the single-DMARD group had achieved remission ($P < 0.009$). At 5 years, the corresponding percentages were 28% and 22% (*P* not significant). The median Larsen radiologic damage scores at baseline, 2 years, and 5 years in the combination-DMARD and single-DMARD groups were 0 and 2 ($P = 0.50$), 4 and 12 ($P = 0.005$), and 11 and 24 ($P = 0.001$), respectively.**

Conclusion. **Aggressive initial treatment of early RA with the combination of 3 DMARDs for the first 2 years limits the peripheral joint damage for at least 5 years. Our results confirm the earlier concept that triple therapy with combinations of DMARDs contributes to an improved long-term radiologic outcome in patients with early and clinically active RA.**

Rheumatoid arthritis (RA) is a chronic, potentially disabling disease characterized by synovial inflammation, with subsequent cartilage and bone destruction leading to joint malalignment. An abundance of evidence indicates the benefits of early intervention with disease-modifying antirheumatic drugs (DMARDs) on the disease course and outcome (1). Some recent studies clearly show that treatment of early RA with combinations of DMARDs is well tolerated and provides better clinical response than treatment with DMARD mono-

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therapy (2–5). In the Dutch Combinatietherapie Bij Reumatoïde Artritis (COBRA) study, the initial aggressive step-down treatment of early RA with high-dose prednisolone, methotrexate, and sulfasalazine for 6 months, in comparison with monotherapy with sulfasalazine, regardless of the subsequent antirheumatic therapy, showed sustained suppression of the rate of radiologic progression that was detectable even after the 4–5-year followup period (6).

We have previously reported the 2-year clinical results of the prospective, randomized Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial comparing the efficacy and tolerability of therapy with a combination of 3 DMARDs with that of DMARD monotherapy in 195 patients with early active RA (4). A total of 178 patients completed the 2-year followup trial. More patients receiving combination therapy than those receiving monotherapy reached clinical remission (37% versus 18%; $P = 0.03$). The increase in Larsen scores was ~2-fold in RA patients in the single-DMARD group compared with those in the combination-DMARD group (4).

The main purpose of this study was to determine whether the relatively high frequency of remissions and slower deterioration of joint damage obtained by the combination therapy at 2 years were sustained despite the unrestricted choice of drug therapy thereafter. We also focused on the safety aspects of the 2 initial DMARD treatment strategies.

PATIENTS AND METHODS

Patients. From April 1993 to May 1995, a total of 199 DMARD-naive patients with recent-onset (symptom duration <2 years; median 6 months) RA were admitted to this multicenter, parallel-group, randomized study comparing the efficacy and tolerability of therapy with a combination of DMARDs (simultaneous sulfasalazine, methotrexate, hydroxychloroquine, and prednisolone) with the efficacy and tolerability of therapy with a single DMARD (initially, sulfasalazine, with or without prednisolone). The study has been described in detail previously (4).

The patient selection criteria were as follows: fulfillment of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for RA (7), age 18–65 years, duration of symptoms <2 years, and active disease, with ≥3 swollen joints and at least 3 of the following 4 features: either an erythrocyte sedimentation rate (ESR) ≥28 mm/hour or a C-reactive protein (CRP) level >19 mg/liter, morning stiffness ≥29 minutes, >5 swollen joints, and >10 tender joints.

Study design during the first 2 years. The treatment was targeted toward remission in all study patients. The combination-DMARD treatment strategy was started with sulfasalazine 500 mg twice daily, methotrexate 7.5 mg/week, hydroxychloroquine 300 mg/day, and prednisolone 5 mg/day as the initial treatment of early RA, but the protocol allowed flexible dosage adjustments to achieve remission, and the highest dosages allowed were 2 gm/day for sulfasalazine, 15 mg/week for methotrexate, and 10 mg/day for prednisolone. If one or several of the components of the drug combination had to be discontinued for any reason, a combination of 3 DMARDs was restarted by replacing sulfasalazine or hydroxychloroquine with auranofin (3–6 mg/day) and replacing methotrexate with azathioprine (2 mg/kg/day), but other DMARDs could also be used as substitutes, as described in detail previously (4).

The single-DMARD treatment strategy was performed according to the "sawtooth" principle (8), by using sulfasalazine (2 gm/day) as the initial DMARD for all patients; the dosage was allowed to be increased up to 3 gm/day. The simultaneous use of up to 10 mg/day of oral prednisolone was allowed for patients with continuously active RA. If an adverse event occurred, or if the clinical response was insufficient, sulfasalazine was replaced with methotrexate. The third recommended DMARD was azathioprine. Intraarticular injections of glucocorticoid were allowed in all patients, according to the judgment of the attending rheumatologist.

Study design from 2 years onward. After 2 years, the choice of DMARD and prednisolone treatments was unrestricted, but the aim of the treatment was still to achieve or maintain remission. Thus, patients in the single-DMARD group who had an insufficient response could also be treated with combinations of DMARDs. Treatment of patients in remission was allowed to be tapered. In the combination-DMARD treatment arm, it was recommended that methotrexate be increased up to 25 mg/week (orally or parenterally) or sulfasalazine up to 3 gm/day if clinically indicated and tolerated. In the original single-DMARD group, a shift toward treatment with DMARD combinations was recommended in patients with active disease.

If the RA was in remission in a patient receiving combination therapy with, for example, sulfasalazine, methotrexate, hydroxychloroquine, and prednisolone, the prednisolone was the first drug to be tapered off (by 2.5 mg/day each month). If the prednisolone could be discontinued without losing remission, then it was recommended that 1 DMARD (either methotrexate or sulfasalazine) be discontinued each year by gradually reducing the dosage (methotrexate by 2.5–5 mg every 3 months or sulfasalazine by 0.5 gm every 3 months). Hydroxychloroquine was the last DMARD to be tapered in RA patients who were in remission. If the RA reactivated, then the last medication with which remission was maintained was reinstituted. The patients were assessed clinically after the initial 2-year followup, at 30, 36, 42, 48, 54, and 60 months.

Ethical considerations. The study was performed according to the principles of the Declaration of Helsinki. The protocol was approved by the national health authorities and ethics committees in all 18 participating hospitals. All patients gave written informed consent.

Methods. The frequency of remissions and the extent of radiologic damage in the joints of the hands and feet were the primary outcome measures. The clinical assessments were made by the treating rheumatologist. Remission was defined

Table 1. Baseline demographic, clinical, and radiographic characteristics of the RA patients who were originally randomized to the combination-DMARD or single-DMARD therapies for 2 years and those who completed the 5-year followup study*

Variable	RA patients who started the trial		RA patients who completed the 5-year followup	
	Combination therapy (n = 97)	Single therapy (n = 98)	Combination therapy (n = 78)	Single therapy (n = 82)
Demographics				
Female, no. (%)	56 (58)	65 (66)	47 (60)	56 (68)
Age, mean ± SD years	47 ± 10	48 ± 10	47 ± 9	48 ± 11
No. (%) RF positive	68 (70)	65 (66)	58 (74)	58 (71)
Disease activity measure, median (IQR)				
ESR, mm/hour	30 (18–49)	35 (21–52)	30 (20–49)	37 (23–55)
No. of swollen joints	13 (8–16)	13 (10–16)	13 (9–16)	13 (10–16)
No. of tender joints	16 (13–24)	17 (13–24)	16 (13–22)	17 (13–24)
Patient's overall assessment, by VAS, mm	49 (30–66)	48 (32–61)	48 (29–64)	47 (32–61)
Physician's overall assessment, by VAS, mm	42 (32–56)	47 (31–62)	42 (32–56)	46 (30–62)
Physical function, by HAQ (0–3 scale)	0.88 (0.50–1.13)	0.88 (0.38–1.25)	0.75 (0.38–1.03)	0.88 (0.38–1.25)
Radiographic assessment				
No. (%) with erosions in the hands or feet	45 (48)	49 (53)	38 (49)	45 (55)
Larsen score, median (IQR)	0 (0–4)	2 (0–7)	2 (0–4)	2 (0–8)

* RA = rheumatoid arthritis; DMARD = disease-modifying antirheumatic drug; RF = rheumatoid factor; IQR = interquartile range; ESR = erythrocyte sedimentation rate; VAS = visual analog scale (0–100 mm); HAQ = Health Assessment Questionnaire.

according to the ACR criteria, as described by Pinals and coworkers (9). However, the patient might or might not have been receiving any drug treatment, and the fatigue (a vaguely defined criterion) and duration definitions were excluded (4). Because the fatigue criterion was excluded, 5 of the 5 ACR remission criteria had to be fulfilled at the appropriate visit before remission was confirmed.

The clinical activity of RA was determined by the Disease Activity Score in 28 joints (DAS28) (10). Radiographs of the hands and feet were taken once a year. The radiographs were evaluated by one of us (LL), an experienced radiologist who was blinded to the clinical data, and were scored according to the method of Larsen et al (11). The range of Larsen scores was from 0 to 210. As secondary outcomes, the frequency of serious adverse events and the frequency of reconstructive joint surgery were assessed.

Statistical analysis. The descriptive values of the variables assessed were expressed as the median and interquartile range (IQR). Variables with normal distribution were tested by Student's *t*-test or analysis of covariance, and variables with non-normal distribution were tested with the Mann-Whitney U test, Wilcoxon's signed rank test, or normal scores test (12). Hommel's adjustment was performed to adjust for multiple testing. Categorical data were analyzed by chi-square test or Fisher's exact test. Logistic regression analysis was used to estimate factors predictive of the achievement of remission at 5 years. An ordered logistic regression analysis was used to estimate the prediction of achieving radiologic progression. The progression of radiologic changes in the hands and feet was tested by the Page test for ordered alternatives and Hodges-Lehmann estimates of the median difference. Radiologic progression was compared by using quantile regression models, with the baseline value as the covariable.

RESULTS

A total of 199 patients with recent-onset RA were originally randomized into 1 of the 2 treatment arms; 195 patients started the treatment (97 taking combina-

Table 2. Medications and treatment strategy during the 5-year followup

Therapy	Original treatment group	
	Combination therapy (n = 78)	Single therapy (n = 82)
Medications, no. (%) of patients		
Prednisolone	78 (100)	67 (82)
Sulfasalazine	78 (100)	82 (100)
Methotrexate	78 (100)	61 (74)
Hydroxychloroquine	78 (100)	49 (60)
Azathioprine	8 (10)	13 (16)
Cyclosporin A	7 (9)	15 (18)
Auranofin	6 (8)	7 (9)
Gold sodium thiomalate	5 (6)	11 (13)
Podophyllotoxin (CPH 82)	2 (3)	3 (4)
D-penicillamine	0 (0)	1 (1)
Leflunomide	0 (0)	1 (1)
Treatment strategy after 2 years, median (IQR) % from the total followup period*		
Single therapy	0 (0–8)	43 (0–100)
Combination therapy	100 (84–100)	37 (0–100)

* IQR = interquartile range.

tion DMARDs and 98 taking a single DMARD). One hundred seventy-eight patients (87 in the combination group and 91 in the single group) completed the 2 years of followup, as described in detail previously (4). At 5 years, 9 patients in the combination group were lost to followup; 4 were in remission, 3 were reluctant to continue followup, 1 changed residences, and 1 died (cardiac event). At 5 years, 9 patients in the single group were also lost to followup; 5 were in remission, 2 died (acute myeloid leukemia; intracerebral and subarachnoid hemorrhage), 1 had an adverse event (chronic obstructive pulmonary disease), and 1 was reluctant to continue followup.

Thus, 5-year followup data were available for 160 RA patients, 78 in the combination group and 82 in the single group. No substantial differences in the baseline demographic and clinical characteristics were found between the patients evaluated at 5 years as compared with the initial cohort (Table 1).

Medical treatment and serious adverse events. After 2 years, 70 of the 78 RA patients in the original combination group continued to receive DMARD combinations. In contrast, various DMARD combinations were taken by 51 of the 82 patients originally allotted to the single-DMARD arm. The proportion of patients in the original combination-DMARD and single-DMARD

Table 3. Serious adverse events occurring during the followup period from year 2 to year 5

Treatment group	Serious adverse event
Combination therapy	
Patient 1	Colon resection, ileostomy, and splenectomy due to Crohn's disease
Patient 2	Deep venous thrombosis of lower extremity after hip arthroplasty
Patient 3	Multiple myeloma
Patient 4	Surgery for carcinoma of prostate
Patient 5	Postoperative myocardial infarction after surgery for stenosis of the lumbar spine
Patient 6	Pneumonia
Patient 7	Sudden death
Patient 8	Nonspecific chest pain
Single therapy	
Patient 1	Death due to acute myeloid leukemia
Patient 2	Death due to intracerebral and subarachnoid hemorrhage
Patient 3	Flare of joint symptoms with fever
Patient 4	Minimal-change nephropathy with nephrotic-range proteinuria due to D-penicillamine therapy
Patient 5	Myocardial infarction; replacement of mitral valve with postoperative infection
Patient 6	Staphylococcal septicemia due to skin infection; non-Q myocardial infarction
Patient 7	Transurethral prostatic resection due to benign prostatic hyperplasia; mobilization of shoulder joint under anesthesia

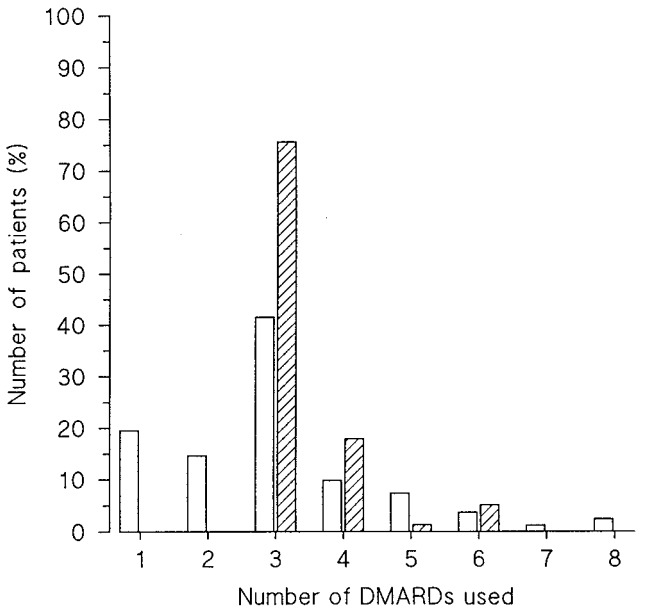

Figure 1. Cumulative number of individual disease-modifying antirheumatic drugs (DMARDs) used during the 5-year followup study of rheumatoid arthritis patients treated with a single DMARD (open bars) or with a combination of DMARDs (hatched bars) for the first 2 years and then with an unrestricted treatment strategy up to year 5.

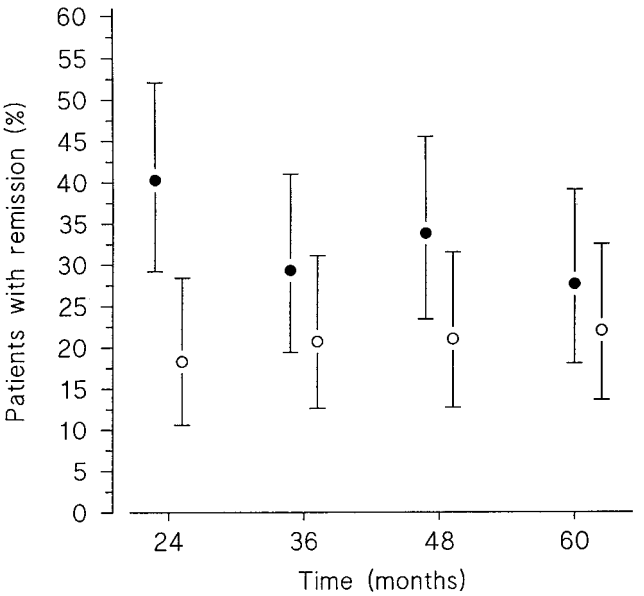

Figure 2. Proportion of rheumatoid arthritis patients in remission at 2 years, during which time they were receiving a single disease-modifying antirheumatic drug (DMARD) (○) or a combination of DMARDs (●). Also shown are the proportions of patients in remission at yearly intervals thereafter, during which time the treatment strategy was unrestricted. Bars show the 95% confidence intervals.

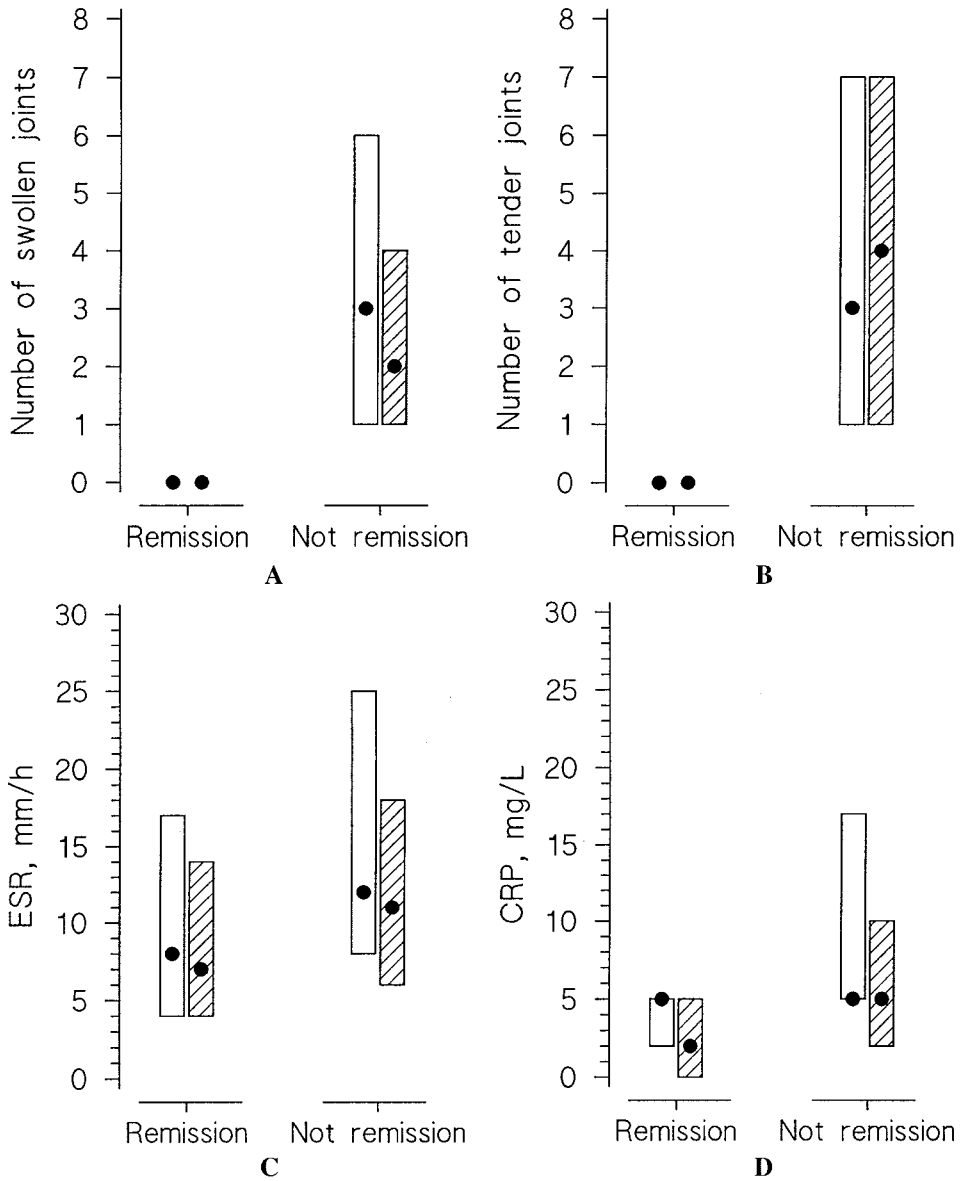

Figure 3. A, Number of swollen joints, **B,** number of tender joints, **C,** the erythrocyte sedimentation rate (ESR), and **D,** C-reactive protein (CRP) level in rheumatoid arthritis patients treated with a single disease-modifying antirheumatic drug (DMARD) (open bars) or a combination of DMARDs (hatched bars), according to the presence and absence of remission at year 5. Bars show the interquartile range; solid circles show the median.

groups who were receiving the combination and single treatments during the followup period between years 2 and 5 are presented in Table 2. The median number of DMARDs taken during the 5-year followup period was 3 in both the original combination group (range 3–6) and the original single group (range 1–8). The numbers of individual DMARDs used are presented in Figure 1 and in Table 2.

The total number of periods treated by various DMARDs during the 5 years was 262 in the combination group and 243 in the single group. The corresponding numbers of cytotoxic DMARDs were 95 and 93, respec-

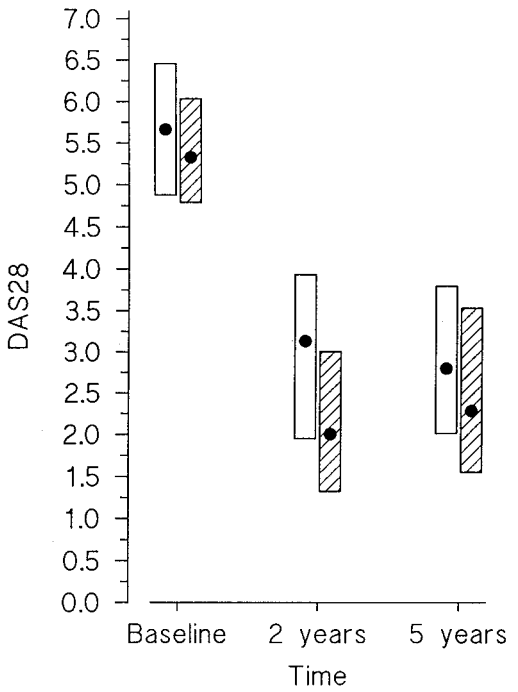

Figure 4. Disease Activity Score in 28 joints (DAS28) at baseline and at years 2 and 5 of therapy in rheumatoid arthritis patients treated with a single disease-modifying antirheumatic drug (DMARD) (open bars) or a combination of DMARDs (hatched bars) for the first 2 years and then with an unrestricted treatment strategy up to year 5. Bars show the interquartile range; solid circles show the median.

tively. None of the patients were treated with biologic agents. There were no significant differences in the occurrence of severe adverse events between the combination-DMARD and single-DMARD groups during the period between year 2 and year 5 (Table 3).

Clinical response, including the proportion of remissions. At 2 years, the proportion of patients whose RA was in remission was significantly higher in the combination group than in the single group (40% [95% confidence interval (95% CI) 29–52] versus 18% [95% CI 11–28]; $P < 0.009$). After 2 years, the frequency of remissions tended to remain higher in the original combination group than in the single group: at 3 years, 29% (95% CI 19–41) versus 21% (95% CI 13–31); at 4 years, 34% (95% CI 23–45) versus 21% (95% CI 13–32); and at 5 years, 28% (95% CI 18–39) versus 22% (95% CI 14–33). At these time points, however, the differences no longer reached statistical significance ($P = 0.41$, $P = 0.21$, and $P = 0.41$, respectively) (Figure 2).

The remission criteria we used were strict. The patients were required to have no tender or swollen joints, as shown for the 5-year followup data presented in Figure 3. Moreover, the ESR and serum CRP levels were low, even in RA patients who were not in remission (Figure 3). The median DAS28 scores in the combination and single groups were as follows: at baseline, 5.33 (IQR 4.79, 6.04) and 5.67 (IQR 4.88, 6,46) ($P = 0.15$); at 2 years, 2.00 (IQR 1.32, 3.00) and 3.13 (IQR 1.95, 3.93) ($P = 0.005$); and at 5 years, 2.28 (IQR 1.55, 3.53) and 2.80 (IQR 2.01, 3.80) ($P = 0.048$), respectively (Figure 4). The time-weighted mean ± SD DAS28 area under the curve from baseline up to 5 years was 2.70 ± 1.07 in the combination group and 3.40 ± 1.06 in the single group ($P < 0.001$).

In logistic regression analyses including sex, age, duration of symptomatic period before diagnosis as well as the number of tender and the number of swollen joints, presence of serum rheumatoid factor, ESR at baseline, and treatment strategy during the first 2 years,

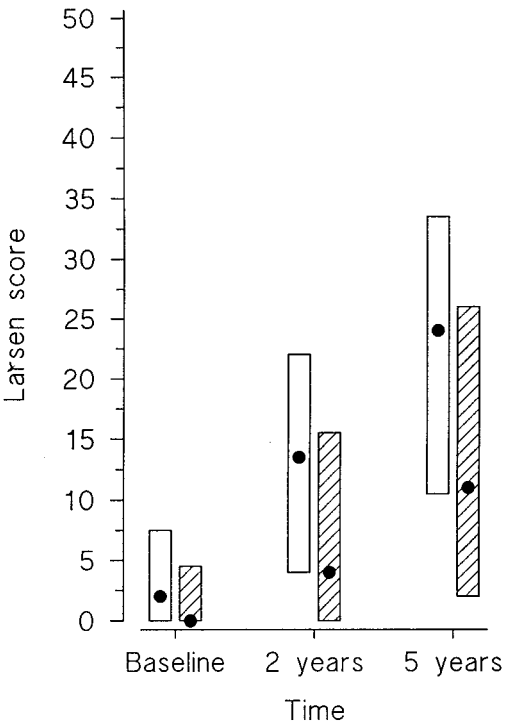

Figure 5. Radiologic progression of rheumatoid arthritis in the hands and feet, as measured by the Larsen scoring system (median and interquartile range [IQR]), at baseline and at 2 and 5 years of therapy in patients treated with a single disease-modifying antirheumatic drug (DMARD) (n = 72 patients) or a combination of DMARDs (n = 72 patients) for the first 2 years and then with an unrestricted treatment strategy up to year 5. Results represent all patients for whom all radiographs were available. Bars show the IQR; solid circles show the median.

Table 4. Ordered logistic regression analysis for the odds of radiologic progression at 5 years*

Variable at beginning of study	Odds ratio (95% CI)	*P*
Rheumatoid factor positivity	2.75 (1.46–5.17)	0.002
Single-therapy versus combination-therapy strategy for 2 years	2.53 (1.44–4.45)	0.001
Disease duration before diagnosis, months	1.11 (1.04–1.17)	0.001
Erythrocyte sedimentation rate, mm/hour	1.02 (1.00–1.03)	0.010
Tender joint count	1.02 (0.98–1.06)	0.316
Age, years	0.99 (0.96–1.02)	0.420
Swollen joint count	0.99 (0.93–1.05)	0.777
Female sex	0.74 (0.41–1.32)	0.308

* Radiologic progression was determined according to the Larsen system (categories of Larsen scores were 0, 1–4, 5–9, and ≥10). 95% CI = 95% confidence interval.

no predictive factors for remission at 5 years were found (data not shown).

Radiologic progression. During the first 2 years, the increase in the median Larsen score was significantly delayed in patients receiving combination DMARDs compared with patients receiving a single DMARD (Figure 5). Although the DMARD treatment was unrestricted after 2 years, radiologic progression was consistently lower in the patients originally randomized into the combination treatment as compared with the patients in the single-treatment group. The median (IQR) number of eroded joints seen on radiographs of hands and feet of patients in the combination and single groups were as follows: at baseline, 0 (0–2) and 1 (0–3); at 2 years, 2 (0–5) and 4 (2–7); and at 5 years, 3 (1–7) and 6 (3–11), respectively. The difference in the change in the number of eroded joints between the study groups was statistically significant ($P = 0.008$).

The extent of radiologic damage in the hands and feet, as measured by the Larsen score (median [IQR]), in the combination and single groups was as follows: at baseline, 0 (0–5) and 2 (0–6) ($P = 0.50$); at 2 years, 4 (0–13) and 12 (4–20) ($P = 0.005$); and at 5 years, 11 (2–26) and 24 (10–34) ($P = 0.001$), respectively (Figure 5). There was a trend toward an increase in radiologic progression in both the combination group (median change in the Larsen score 14 [95% CI 11–19]) and the single group (median change in the Larsen score 20 [95% CI 17–24]), which was significant in both groups ($P < 0.001$ versus baseline). The increase in the Larsen score was statistically significantly lower in the patients included in the combination group compared with those in the single group ($P = 0.004$). The baseline adjusted radiologic progression was also significantly lower in RA patients in the combination group than in the single group ($P = 0.003$), with a benefit of combination-DMARD treatment over single-DMARD treatment of 33% (95% CI 15–50).

In ordered logistic regression analyses, the extent of joint damage in the hands and feet at 5 years was predicted by the presence of serum rheumatoid factor at baseline (odds ratio [OR] 2.75 [95% CI 1.46–5.17]), single-treatment strategy for the first 2 years (OR 2.53 [95% CI 1.44–4.45]), disease duration before diagnosis (OR 1.11 [95% CI 1.04–1.17]), and the ESR at baseline (OR 1.02 [95% CI 1.00–1.03]) (Table 4).

Reconstructive surgery. During the 5-year followup period only 2 patients in the combination group underwent reconstructive surgery (arthrodesis of the subtalar joint and first metatarsophalangeal joints, resection of the heads of the second through the fifth metatarsals, and arthroplasty of the hip joint in one patient; arthrodesis of the wrist joint in the other patient). Seven patients in the single group underwent reconstructive surgery during this time (arthrodesis of the first metatarsophalangeal joint in 1, arthrodesis of the first metatarsophalangeal and subtalar joints in 1, arthrodesis of the subtalar joint in 1, arthrodesis of the wrist joint in 1, resection of the head of the second through the fifth metatarsals in 1, arthroplasty of the hip joint in 1, and arthroplasty of both hip joints in 1). Nevertheless, the difference in the frequencies of reconstructive surgeries between the study groups did not reach statistical significance ($P = 0.17$).

DISCUSSION

The ultimate goal of treating RA is to induce complete remission. If remission is not achieved, then the management goals are to control disease activity, retard the progression of tissue damage, alleviate pain, maintain functional capacity as well as the capacity for employment, and maximize quality of life (1). The rate of spontaneous remissions is estimated to be 14%, and with conventional single-DMARD therapy, the rate of remissions increases to ~18% (13). In a Finnish study of patients with early RA treated according to the "sawtooth" strategy (8), remission was attained in 27% of patients after 2 years of treatment, and after a followup of 5–6 years, the rate of remissions remained stable at 31% (14). The highest rate of remissions reported thus far was achieved by a combination of cyclophosphamide, azathioprine, and hydroxychloroquine (15). This combi-

nation, however, was too toxic for the long-term treatment of RA.

In the present FIN-RACo study, the rate of remissions at 2 years was 40% in DMARD-naive patients with early RA treated with combinations of 3 DMARDs for the first 2 years. However, the lifting of treatment restrictions after 2 years resulted in a decrease in the rate of remissions (28% at 5 years). In patients who were initially treated with a single DMARD for the first 2 years and who had the option to receive DMARD combinations thereafter, the rate of remissions remained stable (18% at 2 years and 22% at 5 years). The results imply that the revocation of therapy with combinations of DMARDs after 2 years was not prudent, since the high remission rate was partly lost. The results also imply that the "late" institution of DMARD combinations (after 2 years from the time of diagnosis) does not increase the rate of remissions in patients who are initially treated with a single DMARD; that is, the therapeutic "window of opportunity" (16,17) appears to be lost in most of these patients. In a recent study (18), we showed that a delay of a few months from the onset of symptoms to the institution of DMARD therapy decreased the ability of the traditional single-DMARD therapy to induce remission in our patients. In essence, we are looking for disease control rather than true disease remission (i.e., remission without DMARD or prednisolone therapy), since practically all of our patients required DMARD therapy in order to have sustained control of the RA. In RA patients with more advanced disease, eroded joints are often tender because of damage and not because of disease activity, and the remission rate may therefore be declining in patients with longer disease duration.

The "window of opportunity" concept is also supported by long-term observational studies. In a 15-year followup study of 135 RA patients with early disease (19) who were treated with DMARDs according to the "sawtooth" strategy for a total of 1,401 person years and including 528 DMARD periods, remission was the reason for DMARD withdrawal in only 32 of them (6.1%). Furthermore, remission was obtained only during the first 3 DMARD periods (19).

Joint erosions seen on radiographs reflect permanent tissue damage and are probably the most objective outcome measure of RA. Long-term followup studies of RA have shown that radiologic damage in patients treated conventionally with DMARDs progresses at a constant rate (20,21). In a 20-year followup study of 103 patients with recent-onset seropositive RA collected during the years 1973–1975, the median annual progression of small joint destruction was 2–3%, and at 20 years, a total of 36% of the patients had achieved a Larsen score of >50 on a scale of 0–100 (22).

Development of erosions in RA appears to be most rapid during the first 2–3 years after the diagnosis (20,23–27). However, the progression of joint destruction in RA patients is retarded by the use of DMARDs. Sokka et al (28) compared the radiologic progression of joint damage for 8 years in 3 cohorts of patients with early RA treated either with conventional monotherapy (gold sodium thiomalate, chloroquine, or D-penicillamine) or monotherapy with 8 various DMARDs, as well as with various DMARD combinations, according to the "sawtooth" treatment strategy. They found a lower rate of destruction in the peripheral joints of RA patients in the more extensively treated cohort. Albers et al (29) reported a comparison of 4 different European inception cohorts encompassing patients with early RA. The patients were treated independently according to aggressive, intermediate, or conservative strategies. The investigators confirmed that early aggressive treatment with DMARDs resulted in not only a more rapid reduction of disease activity, but also a lower rate of radiographic progression over the long term (29). In fact, increasing evidence from randomized controlled trials as well as from long-term observational studies indicates that several DMARDs and biologic antirheumatic agents have antierosive potential (30–32). Moreover, the earlier the DMARD therapy is instituted the more beneficial the effect on radiologic outcome appears to be (33).

The superiority of combination therapy over single therapy in the FIN-RACo trial (4) has been confirmed by other studies with regard to the short-term clinical outcome of patients with early RA (3,5). These findings have resulted in increased optimism with regard to the ability of DMARD combinations to reduce structural joint damage as well, even over the long term.

In fact, the treatment concept appears to work. In the COBRA trial (2), radiologic progression at 80 weeks was significantly lower in patients originally assigned to the combination treatment (COBRA) group as compared with that in patients initially assigned to the sulfasalazine treatment group. More important, after week 80, no strict treatment protocol was followed, but the patients were treated according to the judgment of their own rheumatologists and study nurses. Nevertheless, during the 4–5-year followup period, the annual progression rate according to the Sharp score was 8.6 points in the original sulfasalazine group compared with 5.6 points in the original COBRA group (6). Thus,

significant progression of radiologic damage took place in both study groups ($P = 0.001$), but the mean change was 35% lower in the COBRA group ($P = 0.03$), a proportion consistent with the results of the present study.

Accordingly, the results of the FIN-RACo trial showed that radiologic progression during the first 2 years was significantly reduced not only in peripheral joints (4), but also in the cervical spine (34) of patients treated according to the combination strategy compared with those treated according to the single strategy. The results of the present followup study demonstrate convincingly that radiologic progression continued to be significantly retarded (actually by 33%) at 5 years in RA patients originally allocated to the combination strategy as compared with those originally allocated to the single strategy, despite the lifting of restrictions on DMARD treatment after 2 years. Although the radiologic evidence of joint damage in the hands and feet progressed throughout the 5-year study period in both study groups, the slope for the combination group was statistically significantly more gentle than that for the single group. Only 2 patients in the combination group and 7 in the single group needed reconstructive surgery during the trial. This difference favored the combination group, although the difference was not statistically significant.

Serious adverse events were few and, except for 1 patient in the single-DMARD group (minimal change glomerulonephritis and nephrotic syndrome due to D-penicillamine), the adverse events were most probably not directly related to the drug therapy. Nevertheless, we need more data regarding how strictly we should stick to DMARD combinations in populations of patients with more generalized early RA. Furthermore, more information about the long-term benefits as well as safety issues of the treatment strategy is needed.

In this study, we have shown that early institution of DMARD combinations in patients with clinically active RA is favorable not only in terms of clinical disease activity, but also in terms of long-term radiologic progression. During recent years, the use of new, very expensive biologic antirheumatic drugs has become routine in clinical settings. Prospective studies comparing the effects, including the cost-effectiveness, of combinations of traditional DMARDs with the effects of biologic drugs in patients with early RA are urgently needed.

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REFERENCES

1. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum 2002;46: 328–346.
2. Boers M, Verhoeven AC, Markusse HM, van der Laar MA, Westhovens R, van Denderen JR, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309–18.
3. Calgureni M, Pay S, Caliskaner Z, Apras S, Kiraz S, Ertenli I, et al. Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol 1999;17: 699–704.
4. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet 1999;353:1568–73.
5. O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:1164–70.
6. Landewe RB, Boers M, Verhoeven A, Westhovens R, van der Laar MA, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis. Arthritis Rheum 2002;46: 347–56.
7. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
8. Fries JF. Re-evaluating the therapeutic approach to rheumatoid arthritis: the "sawtooth" strategy. J Rheumatol Suppl 1990;22: 12–5.
9. Pinals RS, Masi AT, Larsen RA, and the Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308–15.
10. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
11. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn (Stockh) 1977;18:481–91.

12. Lehmann EL. Nonparametrics: statistical methods based on ranks. San Francisco: Holden-Day; 1975.
13. Wolfe F, Hawley D. Remission of rheumatoid arthritis. J Rheumatol 1985;12:245–52.
14. Mottonen T, Paimela L, Ahonen J, Helve T, Hannonen P, Leirisalo-Repo M. Outcome in patients with early rheumatoid arthritis treated according to the "sawtooth" strategy. Arthritis Rheum 1996;39:996–1005.
15. Csuka ME, Carrera GF, McCarty DJ. Treatment of intractable rheumatoid arthritis with combined cyclophosphamide, azathioprine, and hydroxychloroquine: a followup study. JAMA 1986;255: 2315–9.
16. O'Dell JR. Treating rheumatoid arthritis early: a window of opportunity. Arthritis Rheum 2002;46:283–5.
17. Landewe RB. The benefits of early treatment in rheumatoid arthritis: confounding by indication, and the issue of timing. Arthritis Rheum 2003;48:1–5.
18. Mottonen T, Hannonen P, Korpela M, Nissila M, Kautiainen H, Ilonen J, et al, for the FIN-RACo Trial Group. Delay to institution of therapy and induction of remission using single-drug or combination–disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum 2002;46:894–8.
19. Sokka T, Hannonen P. Utility of disease modifying antirheumatic drugs in "sawtooth" strategy: a prospective study of early rheumatoid arthritis up to 15 years. Ann Rheum Dis 1999;58:618–22.
20. Kaarela K, Kautiainen H. Continuous progression of radiological destruction in seropositive rheumatoid arthritis. J Rheumatol 1997;24:1285–7.
21. Hulsmans HM, Jacobs JW, van der Heijde DM, van Albada-Kuipers GA, Schenk Y, Bijlsma JW. The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum 2000;43:1927–40.
22. Jantti J, Kaarela K, Belt E, Kautiainen H. Incidence of severe outcome in rheumatoid arthritis during 20 years. J Rheumatol 2002;29:688–92.
23. Larsen A, Thoen J. Hand radiography of 200 patients with rheumatoid arthritis repeated after an interval of one year. Scand J Rheumatol 1987;16:395–401.
24. Mottonen T. Prediction of erosiveness and rate of development of new erosion in early rheumatoid arthritis. Ann Rheum Dis 1988; 47:648–53.
25. Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol 1989;16:585–91.
26. Van der Heijde DM, van Leeuwen MA, van Riel PL, Koster AM, van 't Hof MA, van Rijswijk MH, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 1992; 35:26–34.
27. Paimela L. The radiographic criterion in the 1987 revised criteria for rheumatoid arthritis: reassessment in a prospective study of early disease. Arthritis Rheum 1992;35:255–8.
28. Sokka TM, Kaarela K, Mottonen TT, Hannonen PJ. Conventional monotherapy compared with a sawtooth treatment strategy in the radiographic progression of rheumatoid arthritis over the first eight years. Clin Exp Rheumatol 1999;17:527–32.
29. Albers JM, Paimela L, Kurki P, Eberhardt KB, Emery P, van 't Hof MA, et al. Treatment strategy, disease activity, and outcome in four cohorts of patients with early rheumatoid arthritis. Ann Rheum Dis 2001;60:453–8.
30. Pincus T, Ferraccioli G, Sokka T, Larsen A, Rau R, Kushner I, et al. Evidence from clinical trials and long-term observational studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. Rheumatology (Oxford) 2002;41:1346–56.
31. Jones G, Halbert J, Crotty M, Shanahan EM, Batterham M, Ahern M. The effects of treatment on radiological progression in rheumatoid arthritis: a systematic review of randomized placebo-controlled trials. Rheumatology (Oxford) 2003;42:6–13.
32. Strand V, Sharp JT. Radiographic data from recent randomized controlled trials in rheumatoid arthritis: What have we learned? Arthritis Rheum 2003;48:21–34.
33. Bukhari MA, Wiles NJ, Lunt M, Harrison BJ, Scott DG, Symmons DP, et al. Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: results from a large observational inception cohort. Arthritis Rheum 2003;48: 46–53.
34. Neva MH, Kauppi MJ, Kautiainen H, Luukkainen R, Hannonen P, Leirisalo-Repo M, et al, for the FIN-RACo Trial Group. Combination drug therapy retards the development of rheumatoid atlantoaxial subluxation. Arthritis Rheum 2000;43:2397–401.