Sustained Remission and Reduced Radiographic Progression with Combination Disease Modifying Antirheumatic Drugs in Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To study sustainability of remission and good treatment response, and the association of both with radiographic progression, in early rheumatoid arthritis (RA) in the Finnish Rheumatoid Arthritis Combination Therapy trial (FIN-RACo).

Methods. Patients were randomized to receive either a combination of disease modifying antirheumatic drugs (DMARD; COMBI, n = 97) or a single DMARD (SINGLE, n = 98). Remission was defined according to modified American College of Rheumatology (ACR) remission criteria and Disease Activity Score 28 joint count (DAS28) < 2.6, and sustained remission as presence of remission at 6, 12, and 24 months. Good treatment response was defined as DAS28 ≤ 3.2 and decrease of DAS28 > 1.2.

Results. In 169 patients with complete data, 33 (42%) COMBI and 18 (20%) SINGLE patients achieved modified ACR remission at 2 years, which was sustained in 11 (14%) COMBI and 3 (3%) SINGLE patients. Fifty-four (68%) COMBI and 37 (41%) SINGLE patients were in DAS28 remission at 2 years, which was sustained in 40 (51%) COMBI and 14 (16%) SINGLE patients. Good treatment response was sustained in 67% of COMBI and 27% of SINGLE patients. Over 2 years, the Larsen score increased by a median of 1 (95% CI 0–2) in patients in sustained DAS28 remission compared to 4 (95% CI 2–16) in patients who were in DAS28 remission at 6 months but lost it later; and by 6 (95% CI 2–10) in patients who were not in remission at 6 months.

Conclusion. A remarkable proportion of patients with early RA treated with combinations of DMARD were in remission at 2 years, and remission was more often sustained compared to patients treated with a single DMARD. Sustained remission protects against radiographic joint damage. (First Release Dec 15 2006; J Rheumatol 2007;34:316–21)

Key Indexing Terms:
REMISSION SUSTAINED REMISSION DISEASE ACTIVITY SCORE 28 JOINT COUNT
EARLY RHEUMATOID ARTHRITIS COMBINATION TREATMENT

Early diagnosis and prompt initiation of disease modifying antirheumatic drugs (DMARD) are needed to reduce structural damage in rheumatoid arthritis (RA). The goal of treatment should be to induce remission[1,2]. The American Rheumatism Association (ARA; now American College of Rheumatology, ACR) remission criteria provided the first efforts to define remission in RA[3]. These criteria are rigorous and include questionable elements such as fatigue[4]. The Disease Activity Score (DAS)[5] and its modified version including a 28-joint count (DAS28)[6] were developed to measure disease activity in patients with RA. DAS28 < 2.6 has been used as a definition of remission in RA[7-10], although with some criticism[11,12]. According to the European League Against Rheumatism (EULAR) treatment response criteria, patients are classified as good responders if the current DAS28 is ≤ 3.2 and there is a decrease of DAS28 > 1.2[13].

In the Finnish RA Combination Therapy trial (FIN-RACo), patients with early RA who were treated with combinations of DMARD achieved modified ACR remission more often than patients treated with a single DMARD. Progression of radiographic joint damage was retarded by the combination therapy[14,15].

Sustainability of remission has rarely been studied until recently[16], and it has not been studied with traditional DMARD. In the FIN-RACo trial, only cross-sectional remission has been reported[1,14]. We analyzed sustainability of

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Accepted for publication October 29, 2006.

remission and good treatment response in the FIN-RACo trial, and their association with radiographic outcome over 2 years.

MATERIALS AND METHODS

Study population. In the FIN-RACo study[14], 195 patients with recent-onset RA were randomized to receive either DMARD combination therapy (COMBI) or DMARD monotherapy (SINGLE). Patients with previous DMARD therapy or who had had glucocorticoid therapy within 2 weeks prior to enrollment were excluded. The inclusion criteria were: age between 18 and 65 years, duration of symptoms < 2 years, active disease with ≥ 3 swollen joints, and at least 3 of the following: erythrocyte sedimentation rate (ESR) ≥ 28 mm/h or C-reactive protein (CRP) > 19 mg/l, morning stiffness ≥ 29 min, > 5 swollen joints, and > 10 tender joints. All patients had to fulfill the ARA criteria for RA[17]. The study procedure has been described in detail[14].

The study was conducted according to 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.

Treatment strategy. The goal of treatment was remission in both groups. In the COMBI group, the initial DMARD were sulfasalazine (SSZ) 500 mg twice daily, methotrexate (MTX) 7.5 mg/week, and hydroxychloroquine (HCQ) 300 mg daily. Prednisolone 5 mg daily was instituted simultaneously with the DMARD. Drug doses were adjusted if the patient did not achieve at least 50% improvement in 2 of the following 3 criteria: number of swollen joints, number of tender joints, and ESR or CRP. The highest doses allowed were SSZ 2 g/day, MTX 15 mg/week, HCQ 300 mg/day, and prednisolone 10 mg/day. SSZ or HCQ could be replaced by auranofin (3–6 mg/day) and MTX by azathioprine (2 mg/kg/day) if these drugs were discontinued for inefficacy or adverse effects.

In the SINGLE arm, treatment was performed according to the "sawtooth" strategy[18,19] with remission as the target. The first DMARD was SSZ 2 g/day, and the dose could be increased up to 3 g/day. Simultaneous oral prednisolone treatment was not mandatory, but it was allowed up to 10 mg/day at the discretion of the treating rheumatologist. SSZ could be replaced by MTX (or other single DMARD) in case of an adverse event or lack of efficacy. Intraarticular glucocorticoid injections were allowed according to the judgment of the attending physician in all patients[14].

Methods. Patients were evaluated at baseline, and at 6, 12, and 24 months. Clinical assessments included tender joint count (68 joints) and swollen joint count (66 joints), duration of morning stiffness (min), physician's and patient's overall assessments and pain on visual analog scales (VAS, 0–100 mm), physical function on patient self-report Health Assessment Questionnaire, ESR, and CRP.

Radiographs of hands and feet were taken at baseline and at 6 and 24 months. Radiographs of 163 patients were available at baseline. Radiographs were assessed by LL, an experienced radiologist, who was blinded to the clinical data. Radiographs were scored according to the Larsen method (0–200)[20] including I–V metacarpophalangeal and I–V proximal interphalangeal joints of both hands, II–V metatarsophalangeal joints, interphalangeal joints of big toes, and wrists (multiplied by 5).

Definition of remission. The ACR remission criteria were defined as no joint swelling or soft tissue swelling of tendon sheaths, no joint tenderness or pain on motion, normal ESR of < 30 in women and < 20 in men, morning stiffness ≤ 15 min, and absence of joint pain by history. The criterion of "no fatigue" was excluded, but all the other 5 criteria had to be fulfilled.

DAS28 remission was defined as DAS28 < 2.6[6,21]. DAS28 was calculated using the formula:

$$\text{DAS28} = 0.56 \times \sqrt{(\text{tender joint count 28})} + 0.28 \times \sqrt{(\text{swollen joint count 28})} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}$$

where GH = patient's general health measured on 100 mm VAS.

Sustained remission indicates remission at 6, 12, and 24 months. Sustainability of remission was expressed as the percentage of patients in sustained remission at each visit.

Definition of good treatment response. Good treatment response was defined according to the EULAR treatment response criteria: current DAS28 < 3.2 and decrease of DAS28 > 1.2 from baseline[13,22,23].

Statistical methods. Results are given as mean (standard deviation) or median (interquartile range), percentages and 95% confidence intervals. Sustainability of treatment response was analyzed using generalized estimating equations (GEE) models with exchangeable correlation structure. Odds ratios with confidence intervals were based in the GEE models. Odds ratios of sustained remission were calculated for the treatment groups (COMBI vs SINGLE), adjusted for baseline disease activity on DAS28.

The median change of the Larsen score from baseline to 2 years is presented with Hodges-Lehmann estimates[24]. Permutation-type analysis of covariance with baseline radiographic scores as covariates was applied for comparison of radiographic progression between the groups concerning remission.

RESULTS

Study population. The original FIN-RACo study included 195 patients, 97 in the COMBI arm, 98 in the SINGLE arm. The mean age of all patients was 47 years, 62% were female, 70% were rheumatoid factor-positive, and 48% had erosions on hand and/or foot radiographs at baseline. The analyses include 169 patients with complete data (79 COMBI, 90 SINGLE) who were assessed for remission and good treatment response at 6, 12, and 24 months (Table 1).

Sustainability of ACR remission. By the modified ACR remission criteria (fatigue excluded), 20 (25%) COMBI patients were in remission at 6 months, of whom 13 and 11 were still in remission at 12 and 24 months, respectively. The corresponding data were 11 (12%), 3, and 3 for the SINGLE patients. Thus, remission was sustained in 11 (14%; 95% CI 7% to 23%) COMBI and 3 (3%; 95% CI 1% to 9%) SINGLE patients (p = 0.013; Figure 1). The odds ratio for COMBI versus SINGLE patients to be in sustained ACR remission was 4.61 (95% CI 1.17–16.99) adjusted for baseline DAS28 values.

Sustainability of DAS28 remission. A total of 52 (66%) COMBI patients were in DAS28 remission (DAS28 < 2.6) at 6 months, of whom 45 and 40 were still in remission at 12 and 24 months, respectively. The corresponding data were 33 (37%), 21, and 14 for the SINGLE patients. Thus, a total of 40 (51%; 95% CI 39% to 62%) COMBI and 14 (16%; 95% CI 10% to 24%) SINGLE patients (p < 0.001) met DAS28 sustained remission criteria (Figures 1 and 2). Figure 2 illustrates the number of patients who were in DAS28 remission at 6, 12, and 24 months, and the proportion of those who continued in DAS28 remission at the next timepoint. The odds ratio for COMBI versus SINGLE patients to be in sustained DAS28 remission was 5.58 (95% CI 2.60–11.55) adjusted for baseline DAS28 values.

Sustainability of good treatment response. A total of 59 (75%) COMBI and 47 (52%) SINGLE patients had a good EULAR treatment response at 6 months. Good treatment response was not achieved in 6 COMBI and 23 SINGLE patients between 6 and 24 months. Accordingly, the sustainability of good treatment response was 67% (95% CI 56% to 77%) in the COMBI and 27% (95% CI 18% to 37%) in the SINGLE patients (p <

Table 1. Demographic variables and disease characteristics in all patients and patients who were included in the analysis of sustained remission over 2 years in the FIN-RACo trial.

	All 195 Patients	169 Patients Analyzed for Sustained Remission		
		Total, 169 patients	COMBI, 79 patients	SINGLE, 90 patients
Mean age, yrs (SD)	47 (10)	47 (10)	46 (9)	48 (10)
Female (%)	121 (62)	106 (63)	47 (60)	59 (66)
Positive rheumatoid factor (%)	136 (70)	120 (71)	58 (73)	62 (69)
Patients with erosions (%)	94 (48)	83 (49)	36 (46)	47 (52)
Duration of symptoms before diagnosis, mo, median (IQR)	6 (4, 10)	6 (4, 10)	6 (4, 9)	7 (4, 11)
Tender joints, median (IQR)	17 (13, 25)	17 (13, 24)	16 (13, 23)	17 (13, 24)
Swollen joints, median (IQR)	13 (9, 16)	13 (9, 16)	13 (9, 16)	13 (9, 16)
Patient global assessment, median (IQR)	48 (31, 64)	47 (29, 61)	47 (28, 61)	47 (31, 61)
Physician global assessment	44 (31, 59)	42 (31, 59)	38 (31, 52)	46 (30, 63)
DAS28, mean (SD)	5.6 (1.0)	5.6 (1.0)	5.4 (0.9)	5.7 (1.1)

IQR: interquartile range, DAS: Disease Activity Score.

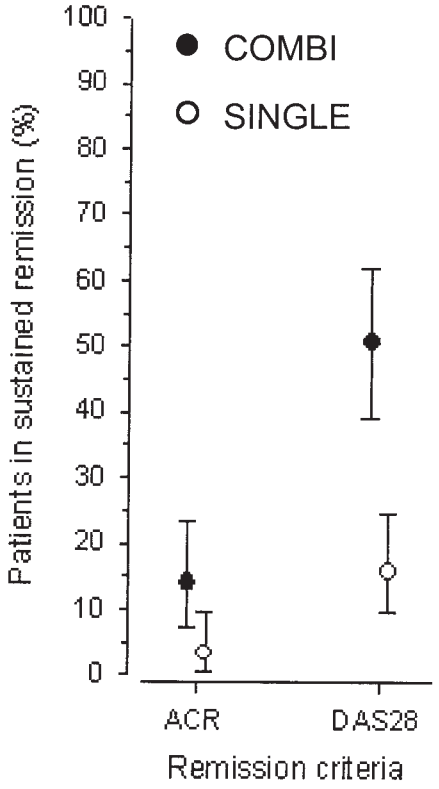

Figure 1. Percentage of patients in sustained ACR remission and DAS28 remission in the COMBI and SINGLE therapy groups in the FIN-RACo trial.

0.001). The odds ratio for COMBI versus SINGLE patients to have sustained good treatment response was 5.38 (95% CI 2.74–10.58) adjusted for baseline DAS28 values.

Radiographic progression and sustainability of remission and good treatment response. The median increase of the Larsen score was 0 (95% CI 0–2) over 2 years in patients with sustained ACR remission; whereas in patients with ACR remission at 6 months but not in sustained remission, the Larsen score increased with a median of 4 points (95% CI 0–10; p = 0.017), and in patients who were not in ACR remission at 6 months the Larsen score increased with a median of 4 points (95% CI 2–8; p = 0.07). In patients with sustained DAS28 remission, Larsen score increased by 1 (95% CI 0–2) during the 2-year followup period, whereas in the patients reaching DAS28 remission at 6 months, but losing it later, the median Larsen score increased by 4 (95% CI 2–16; p < 0.001; Table 2). Radiographs of 6 patients were missing at baseline and were not included in the analyses of radiographic progression. Three of these patients were in sustained DAS28 remission (Table 2).

In patients achieving good EULAR response at all 3 visits, the median Larsen score increased by 1 (95% CI 0–6), compared to 10 (95% CI 4–16; p < 0.001) in patients who achieved good treatment response at 6 months but lost it later, and the median Larsen score increased by median 6 (95% CI 2–10) in patients who did not achieve good treatment response at 6 months (p < 0.001; Table 2).

DISCUSSION

Our analysis of the FIN-RACo study shows that patients in sustained remission had less radiographic progression over 2 years compared to patients who were in remission at 6 months and lost it later; and that sustainability of remission and good treatment response was better in patients who were treated with a combination of DMARD and low-dose prednisolone compared to the monotherapy with or without prednisolone, although treatment was targeted to remission in both groups.

When the ACR criteria for remission were developed in 1981[3] patients with established RA rarely experienced remission[25]. In 1993, when the FIN-RACo study was started, remission was an ambitious outcome in early RA. Nevertheless, as many as 42% of the COMBI patients achieved remission at 2 years, even using a rigorous modification of the ACR remission criteria. Using a more moderate DAS28 < 2.6 as the definition of remission, more than two-thirds of COMBI patients were in remission at 2 years.

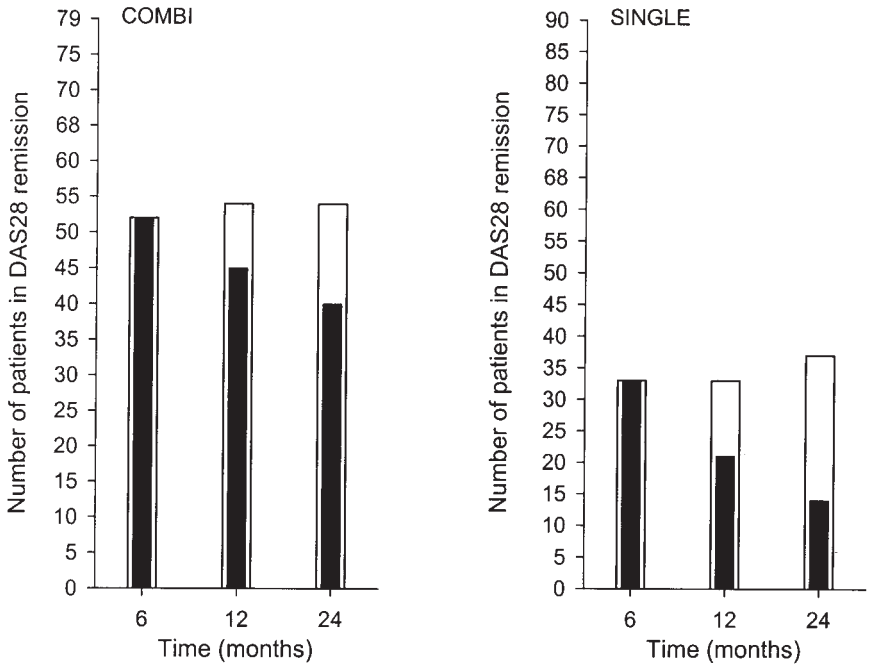

Figure 2. Number of patients in DAS28 remission in the COMBI and SINGLE therapy groups in the FIN-RACo trial (white bars indicate cross-sectional; black bars: patients who were still in remission at the next timepoint).

Table 2. Radiographic progression and sustainability of remission and good treatment response in the 163 pateints of the FIN-the RACo trial with radiographs over 2 years.

Improvement Criteria	No. of Patients	Baseline Larsen Score, Median (IQR)	Change of Larsen Score from 0 to 24 Months, median (95% CI)††	p*
ACR remission				0.017
No remission at 6 months	132	2 (0, 60)	4 (2 to 8)	
Remission at 6 months, no sustained remission	17	2 (0, 8)	4 (0 to 10)	
Sustained remission†	14	0 (0, 3)	0 (0 to 2)	
DAS28 remission				< 0.001
No remission at 6 months	82	0 (0, 4)	6 (2 to 10)	
Remission at 6 months, no sustained remission	30	2 (0, 10)	4 (2 to 16)	
Sustained remission†	51	2 (0, 6)	1 (0 to 2)	
DAS28 good treatment response				< 0.001
No good response at 6 months	62	0 (0, 4)	6 (2 to 10)	
Good response at 6 months; no sustained good response	28	4 (0, 9)	10 (4 to 16)	
Sustained good response**	73	0 (0, 5)	1 (0 to 6)	

† Remission at 6, 12, and 24 months. †† Hodges-Lehmann estimates of median difference. * Permutation-type analysis of covariance. Baseline values are used as covariates. ** Good treatment response at 6, 12, and 24 months.

In the BARFOT study of patients with early RA, remission was also defined as DAS28 < 2.6. Remission rates were lower compared to the FINRACo trial: 29% of patients who were first treated with prednisolone and after 3 months with MTX if needed achieved DAS28 remission at 2 years. In the other treatment arm with SSZ as the initial therapy with or without prednisolone, 19% of the patients met the DAS28 remission criteria at 2 years[26,27].

Van der Heijde, *et al*[16] studied sustainability of DAS and DAS28 remissions and ACR70 responses in the TEMPO trial, comparing the efficacy of the combination of MTX and etanercept to the efficacy of these drugs as monotherapies in

patients with advanced RA. Remission was assessed at 4-week intervals or less frequently over 1 year. Continuity rewarded scoring[28] was used to assess the sustainability of remissions. Patients who were treated with combination therapy managed better than patients who were treated with either of the monotherapies with respect to the number of remission periods and durability of remissions[16]. Similarly, our study shows that in active early RA, combination of traditional DMARD leads to sustained remission more often than DMARD monotherapy.

In the TICORA study[29] the target of intensive therapy was to achieve DAS < 2.4. The intensive strategy was remarkably more beneficial compared to "routine care" with regard to disease activity, radiographic progression, physical function, and quality of life. At 18 months, 65% of patients in the intensive care group were in DAS remission compared to 16% in the routine care group. Similarly to the FIN-RACo trial, control of disease was achieved without the use of anti-tumor necrosis factor treatment in the TICORA study.

Radiographic imaging is the gold standard of assessment of disease progression in RA[30]. In the FIN-RACo trial, the increase of median Larsen score was significantly lower in patients who were treated with combinations of DMARD compared to patients receiving DMARD monotherapy during the first 2 years[15]. We show in this analysis that the Larsen score deteriorates less in patients with early RA who were in sustained remission compared to patients who achieved remission at the 6-month visit but lost it later. Our results are in agreement with studies demonstrating that lower disease activity leads to less radiographic progression[23,31].

A limitation of our study is that we assessed remission only at 6, 12, and 24-month visits. Patients in remission at these timepoints may have experienced active disease between visits. It is known that discontinuation of therapy in remission often leads to rheumatoid flare[32,33]. In our study, combination therapy was continued successfully for 2 years, and half the patients remained in sustained DAS28 remission. Another limitation is that we assessed remission only up to 2 years, although the patients are included in a continuous followup program and the 5-year results have already been published[15]. We chose the 2-year period because after that the choice of treatments was unrestricted.

An explanation for the greater proportion of patients with sustained remission in the COMBI group might be the use of prednisolone. According to the study design all patients in the COMBI group received prednisolone. In the monotherapy arm, prednisolone treatment was at physicians' discretion, and 55 patients (61%) received prednisolone during the 2-year followup time. In the monotherapy group, 8 patients (57%) in sustained remission did not receive prednisolone. The cumulative number of intraarticular glucocorticoid injections was higher in the monotherapy group than in the combination group. Therefore, it appears unlikely that glucocorticoid use would be associated with sustainability of remission in this study[34], although it is conceivable that "artificial" remission can be maintained with glucocorticoids.

RA is a chronic disease leading to severe disability and premature death[35]. Early initiation of therapy is critical for better outcomes[1,36], and therapy with a combination of DMARD is well tolerated and more effective than DMARD monotherapy[14,31,37]. An editorial by van Riel and Fransen was entitled: "To be in remission or not: is that the question?"[38]. The results of our study give reason to modify the question — "To be in *sustained* remission or not, that is the point." We conclude that combination therapy means better sustainability of remission in patients with early RA, and that sustained remission is associated with better radiographic outcomes.

ACKNOWLEDGMENT

The authors thank the other members of the FIN-RACo Trial group: Heikki Julkunen, MD, PhD; Reijo Luukkainen, MD, PhD; Kaisa Vuori, MD; Leena Paimela, MD, PhD; Martti Nissilä, MD, PhD; Urpo Yli-Kerttula, MD, PhD; Kirsti Ilva, MD; Ilppo Pälvimäki, MD; Heikki Piirainen, MD, PhD; Kalevi Koota, MD, PhD; Claes Friman, MD, PhD; Oili Kaipiainen-Seppänen, MD, PhD; Per Franzen, MD; Tapani Helve, MD, PhD; Juhani Koski, MD, PhD; Marianne Gripenberg-Gahmberg, MD, PhD; Riitta Luosujärvi, MD, PhD; and Anna Karjalainen, MD, PhD.

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