Radiographic Progression Is Getting Milder in Patients with Early Rheumatoid Arthritis. Results of 3 Cohorts Over 5 Years

TUULIKKI SOKKA, HANNU KAUTIAINEN, ARJA HÄKKINEN, and PEKKA HANNONEN

ABSTRACT. ***Objective.*** There is a common impression, rarely documented, that the outlook of patients with rheumatoid arthritis (RA) is different today compared to previous decades. We investigated the 5-year radiographic progression of 3 cohorts of patients with early RA enrolled in the 1980s and 1990s.
Methods. Patients with early RA were enrolled into 3 separate studies in 1983-85 (n = 58; Cohort A), 1988-89 (n = 77; Cohort B), and 1995-96 (n = 62; Cohort C) at one rheumatology center; all were subsequently treated actively with disease-modifying antirheumatic drugs according to the "sawtooth strategy" to control inflammation, and monitored regularly to collect data for evaluation of longterm outcome. Evaluation over 5 years included disease activity measures and medications. Radiographs of hands and feet taken at baseline and at 2 and 5 years were analyzed by Larsen score (0–100).
Results. Larsen score increased by a median of 12, 6, and 4 points by Year 5 in cohorts A, B, and C, respectively (p = 0.001), adjusted for age, sex, rheumatoid factor (+/–), and the baseline values for Larsen score and erythrocyte sedimentation rate. RF positivity and persistent high disease activity over 5 years were associated with greater progression of radiographic damage.
Conclusion. Radiographic progression was greatest in the earliest cohort and mildest in the most recent cohort, a phenomenon that was also seen in the literature review. The reasons for the observation may include (1) improved therapy, (2) milder disease, and (3) patient selection. (J Rheumatol 2004;31:1073–82)

Key Indexing Terms:
RHEUMATOID ARTHRITIS LARSEN SCORE RADIOGRAPHS EROSIONS
LONGTERM OUTCOMES LONGITUDINAL OBSERVATIONAL STUDY

Longterm outcomes of patients with rheumatoid arthritis (RA) have improved. Most clinicians with experience of 15–25 years in rheumatology clinics would support this. However, improved longterm outcomes in RA have gained little attention in the literature. Even recent reports regarding outcomes of RA recognize that "RA is a disease characterized by chronic inflammation in multiple joints resulting in joint destruction, functional and work disability, and increased mortality"[1-3]. Indeed, this finding in the early 1980s[4] led to the change of the paradigms of RA[5], and to the call for more aggressive treatment strategies[6-8]. Since then, methotrexate (MTX) in the 1980s[9,10], combinations of disease modifying antirheumatic drugs (DMARD)[11-13], and more recently developed DMARD have been introduced to the treatment of RA. Short-term randomized clinical trials (RCT) with the novel drugs show almost no damage to joints over 1–2 years. Further, there are suggestions that RA is becoming milder[14]. Thus observations about improved longterm outcomes of RA over 5 years or more would be expected.

Luukkainen, *et al*[15] showed 25 years ago that radiographic damage in patients with RA can be retarded over 5 years with early and active therapy with intramuscular gold. Recent results of 2 randomized clinical trials confirm the benefits of early and active therapy on the development of joint destructions in early RA over a 5-year period[16,17].

Observations about improved outcomes of RA over 5 years or more are rare, obviously because RCT cannot be conducted over several years in general. In clinical care, RA usually is assessed qualitatively, which does not allow quantitative comparisons between groups of patients at different periods. Further, even if qualitative longterm data were available, lack of widely accepted methodology to analyze and present the data makes it difficult to report these findings.

Three cohorts of patients with early RA were monitored prospectively over 5 years at Jyväskylä Central Hospital for the periods 1983-85, 1988-89, and 1995-96 with quantitative measures. We report radiographic outcomes of these cohorts over the first 5 years, explore variables associated with radiographic progression, summarize the data concerning the longterm radiographic course of RA illus-

From Jyväskylä Central Hospital, Jyväskylä, Finland; the Department of Rheumatology, Vanderbilt University, Nashville, Tennessee, USA; and the Rheumatism Foundation Hospital, Heinola, Finland.

Supported in part by a grant from the Academy of Finland and Muikkusäätiö.

T. Sokka, MD, PhD, Vanderbilt University and Jyväskylä Central Hospital; H. Kautiainen, BA, Rheumatism Foundation Hospital; A. Häkkinen, PhD; P. Hannonen, MD, PhD, Jyväskylä Central Hospital.

Address reprint requests to Dr. T. Sokka, Department of Rheumatology, Vanderbilt University, 203 Oxford House, Box 5, Nashville, TN 37232-4500. E-mail: tuulikki.sokka@vanderbilt.edu

Submitted September 3, 2003; revision accepted December 2, 2003.

trated in the literature, and discuss reasons for the observed improved outcomes.

MATERIALS AND METHODS

Jyväskylä Central Hospital is the only rheumatology unit to serve the population of 264,000 of the Central Finland district. All new patients with RA are referred to this center for diagnostic studies and initiation of therapies. Over the past 20 years, 3 separate cohorts of patients with early RA were established in this hospital.

Cohort A. The first cohort, 58 patients, was assembled in 1983-85 to study development of erosions in early RA[18]. Inclusion criteria were (1) definite or classical RA[19], (2) no previous use of DMARD, and (3) duration of symptoms < 24 months. The first DMARD was intramuscular gold (IM gold) or hydroxychloroquine (HCQ), and started at the time of enrollment to the study.

Cohort B. The second cohort, 77 patients, was collected in 1988-89 to compare sulfasalazine (SSZ) to placebo[20]. Inclusion criteria were (1) definite or classical RA[19], (2) no previous DMARD, (3) duration of symptoms < 12 months, and (4) active disease; and 2 of the following 3 criteria were required: erythrocyte sedimentation rate (ESR) > 20 mm/h, at least 6 joints with active RA (of 30 assessed), and duration of morning stiffness > 45 minutes. According to the study protocol, half the patients were randomized to receive SSZ, and half started with placebo. However, placebo was replaced with IM gold in 28 patients within the first 6 months due to inefficacy, while 11 other patients were switched to IM gold at one year. One patient never received a DMARD.

Cohort C. The third cohort, 62 patients, was collected in 1995-96 to study benefits of muscle strength exercise in patients with early RA[21]. The inclusion criteria were (1) patient met the American College of Rheumatology (ACR) criteria for RA[22], (2) no previous DMARD, (3) duration of symptoms < 24 months, and (4) age < 65 years. All patients were treated with DMARD from the diagnosis.

Although these studies were started separately with different study hypotheses, all patients were subsequently treated actively with available DMARD according to the sawtooth strategy[7], individually tailored for each patient with a goal of remission. All patients were also monitored regularly to collect data for evaluation of longterm outcomes. The ethics committee of Jyväskylä Central Hospital approved the studies, and patients gave informed consent.

Methods. Clinical examination was undertaken every 6 months during the first 2 years and at irregular intervals (once every 3–12 mo) thereafter, and included laboratory tests [ESR, C-reactive protein (CRP), hemoglobin, and rheumatoid factor (RF) taken one or more times], swollen joint counts (SJC; 28-joint count), radiographs of hands and feet, duration of morning stiffness, and patient questionnaires. To estimate overall disease activity over the first 5 years, the area under the curve (AUC) was calculated for ESR, CRP, and SJC. Unfortunately, during the first 5 years, different questionnaires were used in the cohorts. Therefore, the questionnaire data could not be included in the analyses.

Radiographs of hands and feet were taken in posterior-anterior projection at the beginning of the followup and once a year thereafter. The Larsen score of 0–100 was applied to grade structural damage of the wrists, the first to 5th metacarpophalangeal joints, and the 2nd to 5th metatarsophalangeal joints at 0, 2, and 5 years[23-25]. Joints with a score ≥ 2 were considered erosive. The radiographs were evaluated by author TS, as taught by Dr. Kaarela[26], all radiographs of one patient at the same time, in chronological order, blinded to information concerning patient's disease course, other outcomes, or cohort.

For descriptive statistics, the extent of radiographic progression over 5 years was divided into 3 groups: no progression, severe progression of ≥ 10 Larsen units, and mild progression of 1–9 Larsen units. Division into the 3 groups was based on our clinical view that the extent of damage comparable to the total damage of 2 or more joints (≥ 10 Larsen units) can be regarded as severe.

The starting and ending dates as well as the dose of each DMARD and prednisolone were recorded. To estimate the extent of the therapy, we coded DMARD with numbers 1 to 7, from hypothetically weakest to the strongest: 0 = no DMARD; 1 = HCQ; 2 = single DMARD therapy including D-penicillamine (D-PEN), azathioprine (AZA), cyclosporin A (CYA), auranofin (AURA), and podophyllotoxin (PODO); 3 = IM gold; 4 = SSZ; 5 = combination of DMARD but without MTX; 6 = MTX; 7 = combination of DMARD including MTX. A plain sum of these numbers at years 0, 0.5, 1, 2, 3, 4, and 5 was calculated for each patient, and is denoted the DMARD score. For example, a patient who started SSZ at enrollment, who added MTX at 8 months and IM gold at 26 months, was assigned a score of (4 + 4 + 7 + 7 + 7 + 7 + 7) 43; and a patient who started HCQ at enrollment and was switched to IM gold at 15 months that was discontinued at 3.5 years got a score of (1 + 1 + 1 + 3 + 3 + 0 + 0) 9.

The use of DMARD is illustrated in a bar plot. The bars represent point prevalence of patients taking DMARD at enrollment (time 0) and at the first, second, third, etc, anniversaries after enrollment. Therefore if the patient was not taking a DMARD at that exact anniversary date, DMARD = 0 for that particular timepoint, although the patient may have been taking DMARD other months of that year.

The data of 185 (94%) patients were analyzed. The 5-year data were available for 55, 69, and 61 patients in Cohorts A, B, and C, respectively. Two patients had died in Cohort A and 6 in Cohort B. The 5-year radiographs were not taken in one patient in Cohort A, 2 in Cohort B, and one in Cohort C.

Statistical methods. Data analyses were performed with SPSS 11.0 (SPSS Inc., Chicago, IL, USA) and Stata 8.0 (Stata Corp., College Station, TX, USA) software. The results for continuous variables are given as means (standard deviation, SD) or medians (interquartile range, IQR) and for dichotomous variables as percentages. The differences among the groups were computed by analysis of variance, Kruskal-Wallis test, or chi-square test. A quantile regression model[27] was used to compare radiographic outcomes in the 3 cohorts over 5 years, adjusted for age, sex, RF (+/–), and baseline values for Larsen score and ESR. Hodges-Lehmann estimates with 95% confidence interval (CI) for the change in Larsen score from baseline to 5 years are presented.

A forward conditional median regression model was performed to analyze variables associated with progression of the Larsen score over 5 years, which was the dependent variable in the model. Independent variables included age, cohort, sex, RF (+/–), duration of symptoms, Larsen score at baseline, DMARD score, and AUC for ESR, CRP and SJC.

RESULTS

Comparison of cohorts at baseline and over 5 years. The patient cohorts were similar for age and sex. Percentage of RF+ patients was greatest in Cohort A and lowest in Cohort C, but the difference was not statistically significant. At baseline, ESR, CRP, and duration of morning stiffness were statistically significantly more favorable in the most recent cohort, C, compared to the other cohorts, whereas swollen joint count and pain were greater in Cohort C, but not significantly. The baseline median Larsen score was zero in all cohorts. Over 5 years, inflammatory activity was lowest and medications with DMARD most extensive in Cohort C (Table 1).

Comparison of radiographic progression over 5 years. Progression of Larsen scores in individual patients in the 3 cohorts is shown in Figure 1. Overall, radiographic progression was most prominent in the RF+ patients, and least in Cohort C (Figure 2). Larsen score increased by a median of 12, 6, and 4 by year 5 in cohorts A, B, and C, respectively

Table 1. Demographic and clinical variables at baseline and at 5-year followup in 3 cohorts of patients with early RA.

Variable	Cohort 1983–85 (A) n = 58	1988–89 (B) n = 77	1995–96 (C) n = 62	p value*
At baseline				
No. of women (%)	41 (71)	49 (64)	38 (61)	0.53
Mean (SD) age, yrs	50 (35, 61)	52 (40, 64)	53 (43, 57)	0.24
No. of RF positive patients (%)	46 (79)	53 (69)	38 (61)	0.10
Median (IQR) duration of symptoms, mo	7 (4, 11)	6 (3, 6)	6 (3, 10)	0.01
Median ESR (IQR)	34 (20, 56)	36 (24, 51)	19 (12, 34)	< 0.001
Median CRP (IQR)	16 (8, 40)	14 (7, 36)	4 (1, 12)	0.001
Median SJC (IQR)	4 (2, 8)	3 (1, 7)	5 (3, 9)	0.052
Median morning stiffness (IQR), min	120 (86, 240)	60 (60, 120)	60 (30, 120)	< 0.001
Median pain score (IQR)	NA	33 (20, 45)	42 (26, 60)	0.064
Median Larsen score (IQR), 0–100	0 (0, 2)	0 (0, 1)	0 (0, 1)	0.98
Cumulative variables over 5 years				
Median AUC ESR (IQR)	19 (10, 32)	21 (10, 30)	11 (6, 17)	< 0.001
Median AUC CRP (IQR)	8 (4, 16)	6 (2, 14)	3 (1, 5)	< 0.001
Median AUC SJC28 (IQR)	1 (1, 3)	0 (0, 3)	1 (1, 2)	0.002
Median DMARD score (IQR)	17 (9, 21)	18 (12, 24)	27 (24, 32)	< 0.001
No. of patients taking low-dose prednisolone (%)	20 (35)	21 (27)	32 (52)	0.011

* p values from analysis of variance, Kruskal-Wallis test, or chi square test, when appropriate. SD: standard deviation; IQR: interquartile range; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SJC 28: number of swollen joints on 28 joint count; AUC: area under the curve; DMARD: disease modifying antirheumatic drug; NA = not available.

(p = 0.001), adjusted for age, sex, RF, and the Larsen score and ESR at baseline (Table 2).

Patients who had major radiographic progression (> 10 Larsen units) were more often RF positive, were more often from Cohort A, and had more active disease over the 5 years, compared to patients with none or minor radiographic progression (Table 3). In a forward stepwise median regression analysis, younger age, earlier cohort, higher Larsen score at baseline, and AUC for ESR, CRP and SJC were statistically significant explanatory variables for the progression of the Larsen score over 5 years ($p < 0.01$), while sex, RF status, duration of symptoms, and the DMARD score did not contribute significantly to the model. The model was able to explain 25% of the variation of the progression in Larsen score.

Radiographic progression in RF+ patients. Since RF positivity is a known risk factor for erosions, we describe observations concerning RF+ patients in more detail. The percentage of RF+ patients with erosions increased from baseline to 5 years from 40% to 86% in Cohort A, from 26% to 67% in Cohort B, and from 32% to 73% in Cohort C. Larsen score > 10 was present in 9%, 40%, and 55%; 0%, 20%, and 33%; and 3%, 8%, and 14% of patients at the baseline, at 2 and 5 years, in Cohorts A, B, and C (Table 4). The corresponding proportions of patients with a Larsen score > 20 at 5 years were 39%, 22%, and 3%. Although the extent of joint damage was lowest in patients in Cohort C at 2 and 5 years, the proportion of patients with an erosive disease was similar: at 5 years, 86%, 67%, and 73% of RF+ patients in Cohorts A, B, and C had erosions in their joints, indicating similar potential for an erosive disease in all 3 cohorts.

Therapy with DMARD in the 3 cohorts. Therapy with DMARD was instituted within a median of 7, 6, and 6 months after the start of symptoms in Cohorts A, B, and C, respectively. In Cohort A, the first DMARD was IM gold in 70% and HCQ in 30% of patients. In Cohort B, 50% of patients started SSZ at enrollment. The other half of patients in Cohort B were randomized to get placebo, which was switched to IM gold in most cases within 6 months, and in all cases but one within a year[20]. In Cohort C, almost all patients started with SSZ.

Only a few patients in Cohort A took MTX during the first 5 years, while 6–20% of Cohort B were treated with MTX as single therapy or as part of a combination of DMARD during 2–5 years. In Cohort C, 24%, 50%, and 70% were taking MTX or a combination of DMARD at 6 months, 2 years, and 5 years, respectively (Figure 3). According to the DMARD score, the use of DMARD was most extensive in Cohort C (Table 1).

Thirty-five percent, 27%, and 52% of patients in Cohorts A, B, and C, respectively, took prednisolone with a median dose of 5 mg at least periodically during the 5 years (Table 1).

DISCUSSION

We describe the 5-year radiographic progression in 3

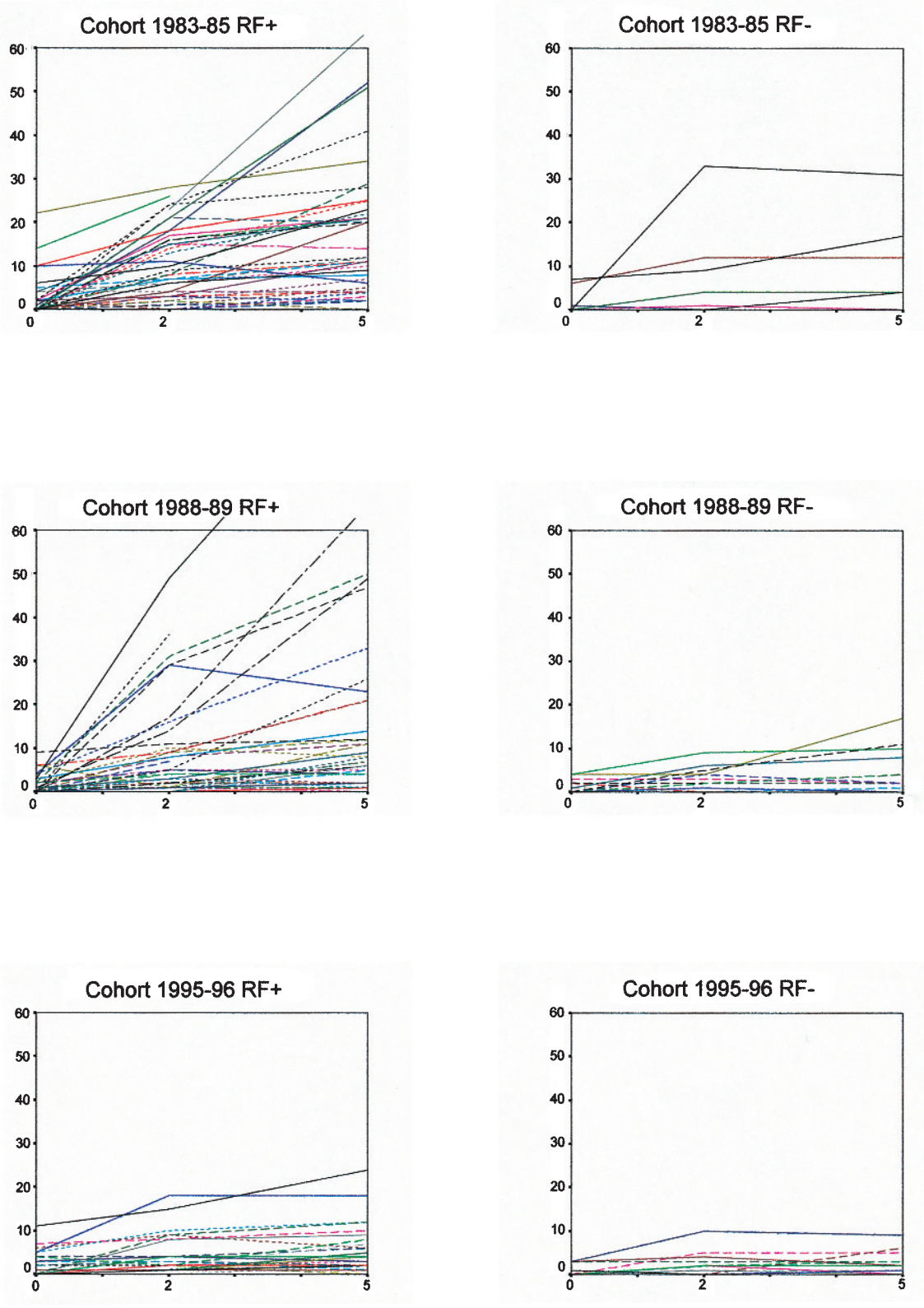

Figure 1. Progression of Larsen scores in patients with early RA over 5 years, according to cohort and RF status (+/–). Each line represents the Larsen score of each patient.

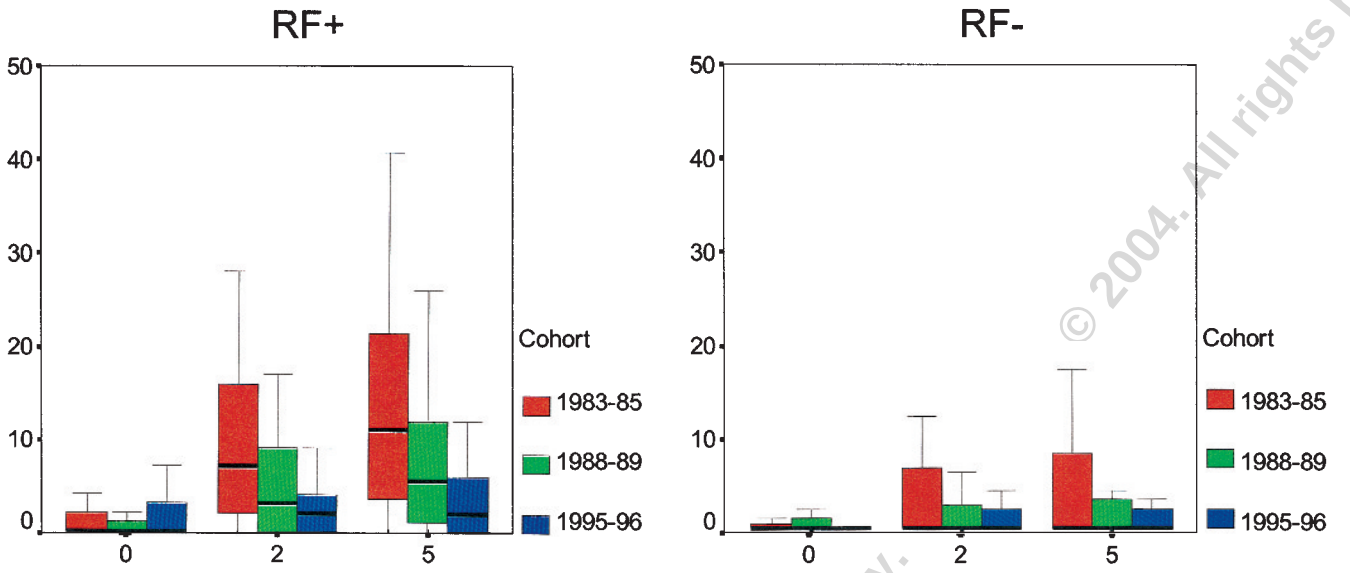

Figure 2. Progression of Larsen scores (0–100, vertical axis) in 3 cohorts of patients with early RA over 5 years (horizontal axis), according to RF status (RF +/–).

Table 2. Comparison of radiographic outcomes over 5 years in 3 cohorts of patients with early RA.

Cohort	Change from Baseline to 5 years, Median (95% CI)*
A 1983–85	12 (8 to 16)
B 1988–89	6 (4 to 11)
C 1995–96	4 (3 to 6)

* Hodges-Lehman estimates of median difference.

cohorts of patients with early RA treated actively with DMARD at different periods of time at one rheumatology center. The main observation is that the progression was greatest in the earliest cohort, and mildest in the most recent cohort of patients. The reasons for our observation may include (1) improved therapy, (2) milder disease, and (3) patient selection. These aspects will be discussed below.

Radiographic outcomes in RA > 5 years in the literature. The general impression of rheumatologists is that the outlook of patients seen in rheumatology clinics has changed over the past 2 decades. A tendency to a more moderate radiographic progression over time can be seen in the literature. We reviewed a selection of cross-sectional and longitudinal observational studies that illustrate radiographic outcomes in RA[25,26,28-39]. Our intention was not to analyze these cohorts in more detail other than to visualize published data concerning radiographic progression over the decades. In our illustrations, erosion scores are presented as percentages of the maximum of the scoring method, scaled 0–100% or 0–40% of the maximum (Figure 4).

Cross-sectional studies of Larsen and Thoen[28], Fuchs, *et al*[29], and Lassere, *et al*[30] indicated erosion scores of 30–50% of the maximum over 10 to 15 years from the onset of disease. Similarly, earlier longitudinal followup studies including patients with early RA since the 1960s to early 1980s showed comparably poor longterm radiographic outcomes[25,31-33]. In these studies, erosion scores were 35–50% of the maximum over 8 to 20 years from onset of disease. In the study by Fex, *et al*[34], the 5-year erosion scores were 27% of the maximum in patients who were treated with DMARD, and 7% in patients with no DMARD therapy, and 27% of maximum at 10 years in all patients[35]. In more recent followup studies of patients with early RA, erosion scores from 7% to 31% of the maximum at 6–12 years from the onset of disease have been reported[26,36-39]. Review of these studies suggests that radiographic progression was more extensive in the earlier reports compared to the most recent ones.

Improved therapy. More extensive use of DMARD in early disease may be one of the reasons for improved radiographic outcomes of RA over the past decades. RCT show that DMARD slow or prevent radiographic damage in RA over 1–2 years[40]. However, only 2 recent RCT have been conducted over 5 years, while RCT in general last for 1–2 years only, for known reasons[41].

In the FinRACo trial comparing the effectiveness and tolerability of a combination of MTX, SSZ, HCQ, and prednisolone with a single DMARD (initially SSZ) +/– prednisolone for 2 years, the patients who received combination therapy had erosion scores of 5% of the maximum at 5 years, compared to 11% of the maximum in those who received monotherapy[16]. Similar results have been reported in the COBRA trial[17]. Although direct comparisons are unjustified, it is worth noting that the 5-year median changes

Table 3. Comparison of demographic and clinical variables in 3 groups according to the extent of radiographic progression over 5 years. Values are mean (SD) or percentages.

Variable	Extent of Radiographic Progression			
	None n = 72	1–9 Larsen Units n = 72	≥ 10 Larsen Units, n = 41	*p value
Age, yrs	49.3 (13.5)	51.5 (12.7)	45.5 (16.1)	0.087
Sex, % female	65.3	61.1	75.6	0.29
RF, % positive	48.6	76.4	90.2	< 0.001
Cohort				
1983–85 A, %	23.6	34.8	57.4	
1988–89 B, %	34.8	43.5	37.7	< 0.001
1995–96 C, %	41.8	21.7	4.9	
		Median (IQR)		
Clinical variables at time of diagnosis				
Duration of symptoms, mo	5 (3, 8)	6 (4, 9)	6 (4, 10)	0.82
ESR	22 (14, 35)	35 (20, 50)	38 (28, 53)	0.26
CRP	5 (2, 14)	14 (4, 37)	16 (7, 37)	0.90
Hemoglobin	134 (124, 143)	133 (124, 142)	125 (121, 134)	0.027
SJC 28	3 (2, 7)	5 (3, 9)	4 (2, 8)	0.25
Morning stiffness	60 (20, 120)	105 (60, 180)	120 (60,180)	0.33
Larsen score (0–100)	0 (0, 0)	0 (0, 2)	0 (0, 4)`	0.13
Cumulative variables over 5 years				
AUC ESR	10 (5, 16)	17 (10, 28)	25 (18, 37)	0.001
AUC CRP	3 (1, 5)	4 (2, 14)	12 (7, 29)	< 0.001
AUC SJC28	1 (0, 1)	1 (0, 3)	3 (2, 5)	< 0.001
DMARD score	21 (13, 27)	22 (17, 28)	20 (15, 27)	0.17

* p values from analysis of variance, Kruskal-Wallis test or chi square test, when appropriate. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SJC 28: number of swollen joints on 28 joint count; AUC: area under the curve; DMARD: disease modyfying antirheumatic drug.

Table 4. Radiographic outcomes of rheumatoid factor positive patients over 5 years in 3 cohorts of patients with early RA.

	Cohort		
	A 1983–85 n = 46	B 1988–89 n = 53	C 1995–96 n = 38
Patients with Larsen score ≥ 10, %			
Baseline	8.7	0.0	2.6
2 yrs	40.0	20.4	7.9
5 yrs	54.5	32.6	13.5
Patients with erosions, %			
Baseline	40.0	26.4	31.6
2 yrs	77.8	57.1	57.9
5 yrs	86.4	67.4	73.0

in the Larsen score (0–100) of 12, 6, and 4 in our patients in cohorts A, B, and C, respectively, are similar to those in patients in the recent randomized clinical trials.

The 5-year evaluation of the Utrecht Arthritis Cohort Study could not show benefits of early DMARD therapy including IM gold, HCQ, or MTX (7.5–15 mg) for a year compared to the "pyramid" approach, which included no DMARD during the first year[42]. The article and the accompanying editorial[43] state that the early DMARD strategy in this study may not have been aggressive enough compared to a pyramid strategy. Nevertheless, radiographic damage of < 5% over 5 years in that study is among the lowest ever reported.

A consensus how to report and compare the extent of longitudinal use of DMARD in clinical care does not exist. Percentage of patients who take compared to those who do not take DMARD at certain timepoints has been reported[26,34], but may be a crude measure at this time. Proportion of time "on any DMARD"[44] may not provide an accurate estimate of the extent of the treatment, due to different "powers" of DMARD. Therefore, we developed a DMARD score for this purpose. The possible utility of this or a similar score remains to be proved. Nevertheless, DMARD were used most extensively in the most recent cohort, Cohort C, in our study. Concomitantly, disease activity was lowest and radiographic progression mildest in Cohort C compared to the others (Table 1). More extensive use of DMARD may have contributed to the milder radiographic progression in Cohort C. On the other hand, the DMARD score was similar in patients with greater or milder radiographic progression (Table 3). In retrospect, one might wonder whether patients with a greater progression should have been treated with DMARD more extensively.

Milder disease. It has been suggested that RA is becoming milder[14]. This is hard to prove without quantitative data from rheumatology clinics, which are usually not available, although the rationale and logistics for such a data collection are available. Quantitative data are collected for RCT, but the inclusion criteria for RCT have remained similar over 2 decades[45], and these data are useless to assess whether RA

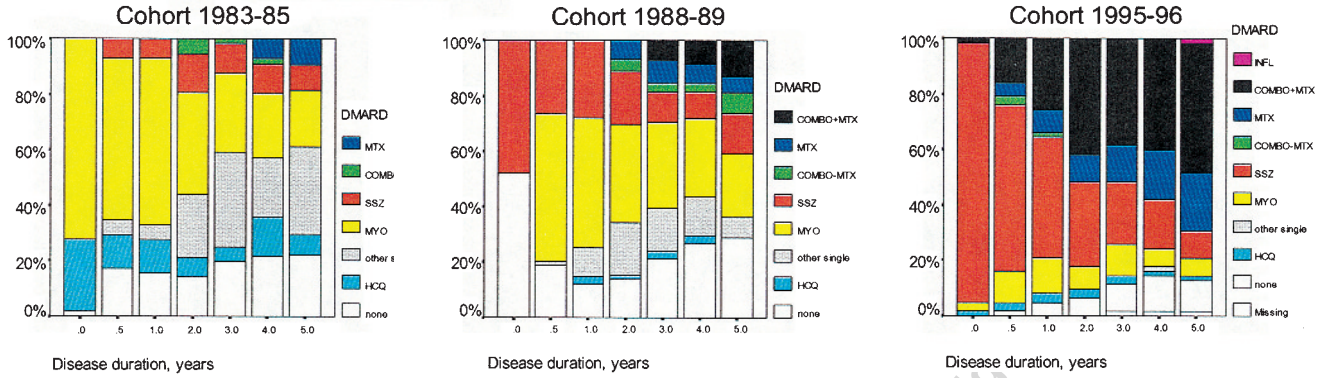

Figure 3. DMARD taken by patients with early RA over 5 years: percentages of patients taking each drug or combination. MTX: methotrexate, COMBO-MTX: combination of DMARD without MTX, SSZ: sulfasalazine, MYO: intramuscular gold, HCQ: hydroxychloroquine, COMBO+MTX: combination of DMARD including MTX, INFL: infliximab.

is becoming milder or not. Further, quantitative data are not available from those who were excluded from RCT.

In this report, disease appeared to be least active at baseline in the most recent cohort, C, which suggests that patients with early RA are doing better at this time compared to earlier decades (Table 1). However, there were no statistically significant differences in SJC or Larsen score between the groups at baseline.

The progression of the Larsen score over 5 years was greatest in Cohort A and least in Cohort C (Table 2). Further, only 14% of Cohort C patients who were RF+ had greater damage (Larsen score ≥ 10) at 5 years, compared to 55% of Cohort A patients (Table 4). Despite the marked difference in the extent of the radiographic damage, the percentage of patients with an erosive disease was similar, 86% compared to 73% of RF+ patients in Cohorts A and C, respectively. Our results also indicate that the patients in the most recent cohort have potential for an erosive disease although the extent of radiographic damage remained low.

Patient selection. The 3 cohorts represent patients with early RA from the same district at different time periods. Inclusion criteria were mostly similar, requiring early RA with duration of symptoms for 1–2 years maximum, and no previous use of DMARD. However, in Cohort B, 2 of 3 disease activity measures were required (ESR > 20 mm/h, ≥ 6 joints with active RA, and morning stiffness > 45 min), and in Cohort C all patients were < 65 years old. Paradoxically, the Cohort B patients did not have the greatest disease activity at baseline, and Cohort C patients were not the youngest (Table 1).

We think that these cohorts represent patients with early RA who met ACR criteria for RA in our district at the time periods the cohorts were enrolled, without major biases. The Jyväskylä Central Hospital statistics indicate that during the enrollment period for the Cohorts A, B, and C, 145, 197, and 157 patients, respectively, were diagnosed with RA. Thus, 39–40% of patients during each period were enrolled in these cohorts.

Factors associated with the extent of radiographic progression. Persistent higher disease activity and RF positivity were associated with greater radiographic progression over 5 years (Table 3), as observed in several other studies[44,46].

Why reports of improved longterm radiographic outcomes are rare. Emerging evidence suggests that radiographic progression in RA can be retarded by early and continuous therapy with DMARD[40]. However, observational studies describing longterm radiographic outcomes in RA are rare. The reasons for relatively few reports might include lack of data: (1) Clinical observations of rheumatologists do not support the theory that longterm radiographic outcomes in RA have been changed. In other words, it is assumed that considerable damage of 30–50% of the theoretical maximum is reached during the first 10 years, and therefore there is no interest to take radiographs. (2) Although the use of DMARD has become more extensive during the last 10 years, individual patients may not have been treated early, continually, and serially with DMARD in general, and thus the potential effect of continual use of DMARD cannot be seen in the long term. (3) Patients are lost to followup and therefore longitudinal observations are impossible in the clinical setting. (4) Radiographs are taken rarely in routine clinical care, and longitudinal data including radiographs are not collected in rheumatology clinics. (5) Further, even if qualitative longterm data were available, lack of widely accepted methodology to present the data makes it difficult to report these findings.

Our results irrevocably indicate that the progression of radiographic damage is getting milder in patients with RA. We hope that our report will encourage other rheumatologists to collect serial longterm data including radiographs, and report their findings to the rheumatology community to confirm or deny our results regarding the observed improved longterm radiographic outcomes of patients with RA.

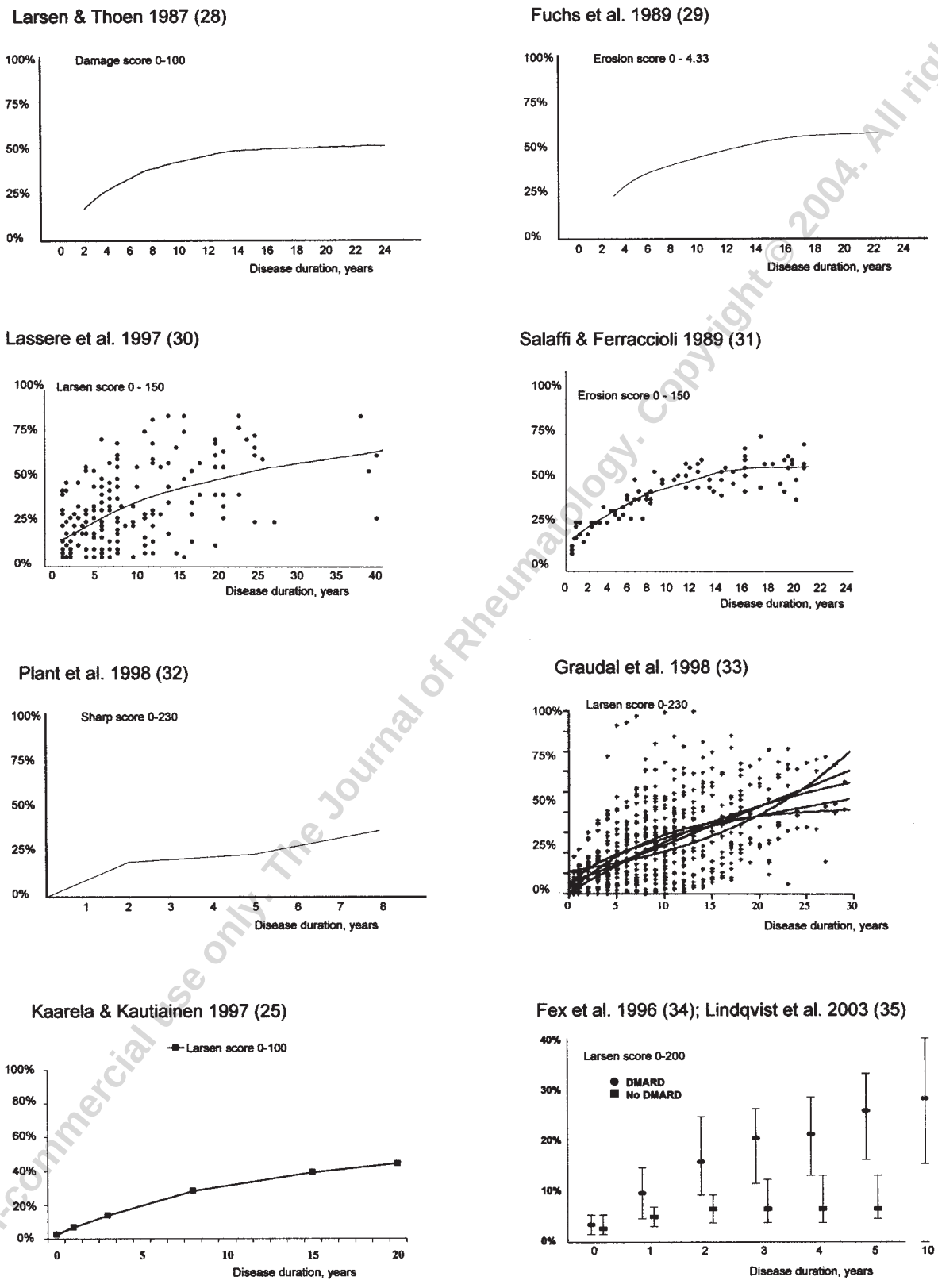

Figure 4. Longterm radiographic progression in patients with RA in selected cross-sectional and longitudinal studies. Erosion scores are presented as percentage of the maximum of the scoring method that was used. With permission: Kaarela, *et al*[25]; Larsen, *et al*[28]; Salaffi, *et al*[31]; Plant, *et al*[32]; Graudal, *et al*[33]; Fex, *et al*[34]; Wolfe, *et al*[37]; Hulsmans, *et al*[39].

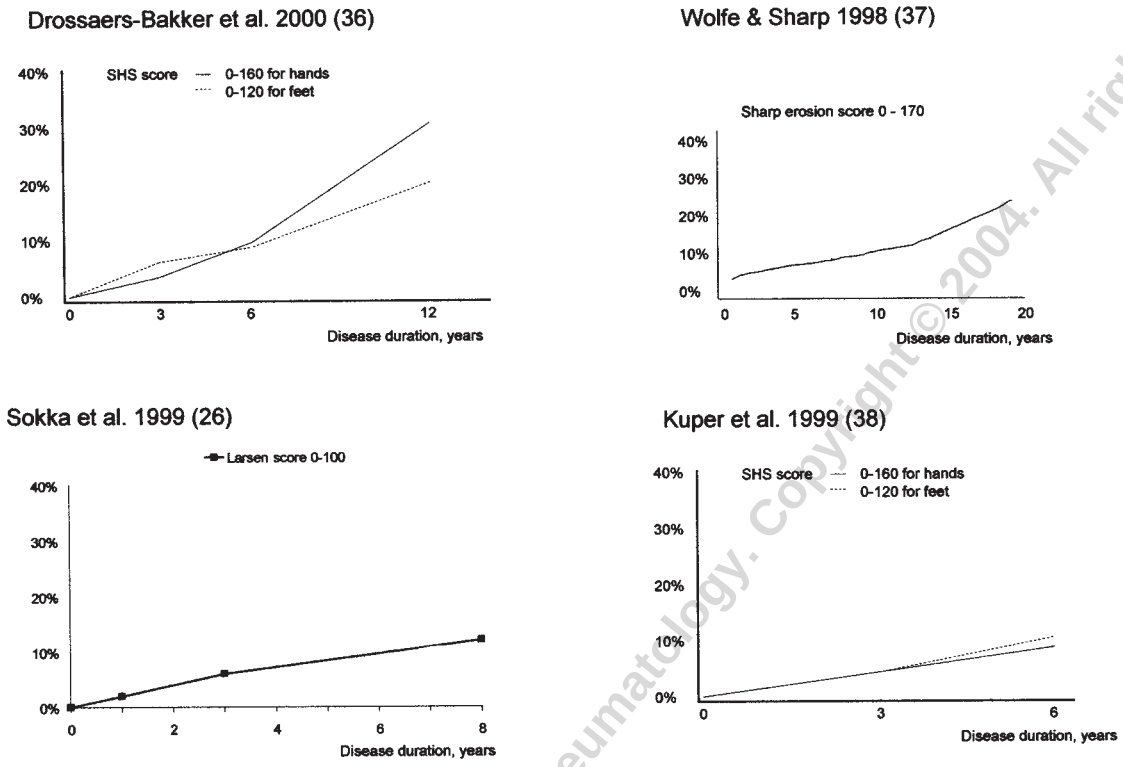

Figure 4. Continued

ACKNOWLEDGMENT

The authors would like to recognize Dr. Timo Möttönen, who was the initial investigator of Cohort A, Dr. Kalevi Kaarela for instruction on analyzing radiographs, Dr. Theodore Pincus for inspiring discussions of the topic, and Research Assistants Sari Leinonen and Jani Saalamo for their help organizing the data.

REFERENCES

1. Mottonen T, Hannonen P, Korpela M, et al. 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.
2. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:614-24.
3. Reece RJ, Kraan MC, Radjenovic A, et al. Comparative assessment of leflunomide and methotrexate for the treatment of rheumatoid arthritis, by dynamic enhanced magnetic resonance imaging. Arthritis Rheum 2002;46:366-72.
4. Pincus T, Callahan LF, Sale WG, Brooks AL, Payne LE, Vaughn WK. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. Arthritis Rheum 1984;27:864-72.
5. Pincus T, Callahan LF. Reassessment of twelve traditional paradigms concerning the diagnosis, prevalence, morbidity and mortality of rheumatoid arthritis. Scand J Rheumatol 1989;18 Suppl 79:67-96.
6. Wilske KR, Healey LA. Remodeling the pyramid — a concept whose time has come [editorial]. J Rheumatol 1989;16:565-7.
7. Fries JF. Reevaluating the therapeutic approach to rheumatoid arthritis: the "sawtooth" strategy. J Rheumatol 1990;17 Suppl 22:12-5.
8. Pincus T, Callahan LF. Remodeling the pyramid or remodeling the paradigms concerning rheumatoid arthritis — lessons from Hodgkin's disease and coronary artery disease. J Rheumatol 1990;17:1582-5.
9. Hoffmeister RT. Methotrexate therapy in rheumatoid arthritis: 15 years experience. Am J Med 1983;75 Suppl 6A:69-73.

10. Weinblatt ME, Coblyn JS, Fox DA, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. N Engl J Med 1985;312:818-22.
11. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996;334:1287-91.
12. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309-18.
13. Mottonen T, Hannonen P, Leirisalo-Repo 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.
14. Silman A, Davies P, Currey HLF, Evans SJW. Is rheumatoid arthritis becoming less severe? J Chron Dis 1983;36:891-7.
15. Luukkainen R, Kajander A, Isomäki H. Effect of gold on progression of erosions in rheumatoid arthritis: better results with early treatment. Scand J Rheumatol 1977;6:189-92.
16. Korpela M, Möttönen T, Laasonen L, Kautiainen H, Hannonen P, Leirisalo-Repo M. The impact of initial aggressive drug treatment with DMARDs on the development of joint damage in the long term in patients with rheumatoid arthritis. The 5-year experience from the FIN-RACo study [abstract]. Arthritis Rheum 2001;44 Suppl:S153.
17. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum 2002;46:347-56.
18. Mottonen TT. Prediction of erosiveness and rate of development of new erosions in early rheumatoid arthritis. Ann Rheum Dis 1988;47:648-53.
19. Ropes MW, Bennett GA, Cobb S, Jacox RF, Jessar RA. 1958 revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 1958;9:175-6.
20. Hannonen P, Möttönen T, Hakola M, Oka M. Sulfasalazine in early rheumatoid arthritis. Arthritis Rheum 1993;36:1501-9.
21. Hakkinen A, Sokka T, Kotaniemi A, Hannonen P. A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. Arthritis Rheum 2001;44:515-22.
22. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
23. 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.
24. Larsen A. How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in longterm studies? J Rheumatol 1995;22:1974-5.
25. Kaarela K, Kautiainen H. Continuous progression of radiological destruction in seropositive rheumatoid arthritis. J Rheumatol 1997;24:1285-7.
26. Sokka TM, Kaarela K, Möttönen TT, Hannonen PJ. Conventional monotherapy compared to a "sawtooth" treatment strategy in the radiographic procession of rheumatoid arthritis over the first eight years. Clin Exp Rheumatol 1999;17:527-32.
27. Gould W, Rogers WH. Quantile regression as an alternative to robust regression. Proceedings of the Statistical Computing Section, 1994. Alexandria, VA: American Statistical Association; 1994.
28. 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.
29. 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.
30. Lassere M, Houssien D, Scott D, Edmonds J. Reference curves of radiographic damage in patients with rheumatoid arthritis: Application of quantile regression and fractional polynomials. J Rheumatol 1997;24:1288-94.
31. Salaffi F, Ferraccioli GF. Progress of the anatomical damage in rheumatoid hands. Radiography of the natural course of the disease or of the course during treatment? Scand J Rheumatol 1989;18:119-20.
32. Plant MJ, Jones PW, Saklatvala J, Ollier WER, Dawes PT. Patterns of radiological progression in early rheumatoid arthritis: Results of an 8 year prospective study. J Rheumatol 1998;25:417-26.
33. Graudal NA, Jurik AG, de Carvalho A, Graudal HK. Radiographic progression in rheumatoid arthritis: A long-term prospective study of 109 patients. Arthritis Rheum 1998;41:1470-80.
34. Fex E, Jonsson K, Johnson U, Eberhardt K. Development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. Br J Rheumatol 1996;35:1106-15.
35. Lindqvist E, Jonsson K, Saxne T, Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatic arthritis. Ann Rheum Dis 2003;62:611-6.
36. Drossaers-Bakker KW, Amesz E, Zwinderman AH, Breedveld FC, Hazes JM. A comparison of three radiologic scoring systems for the long-term assessment of rheumatoid arthritis: findings of an ongoing prospective inception cohort study of 132 women followed up for a median of twelve years. Arthritis Rheum 2000;43:1465-72.
37. Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: A 19-year study of radiographic progression. Arthritis Rheum 1998;41:1571-82.
38. Kuper IH, van Leeuwen MA, van Riel PLCM, et al. Influence of a ceiling effect on the assessment of radiographic progression in rheumatoid arthritis during the first 6 years of disease. J Rheumatol 1999;26:268-76.
39. Hulsmans HM, Jacobs JW, van der Heijde DM, 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.
40. Pincus T, Ferraccioli G, Sokka T, 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 2002;41:1346-56.
41. Stein CM, Pincus T. Placebo-controlled studies in rheumatoid arthritis: Ethical issues. Lancet 1999;353:400-3.
42. Verstappen SMM, Jacobs J, Bijlsma JWJ, et al. Five-year followup of rheumatoid arthritis patients after early treatment with disease-modifying antirheumatic drugs versus treatment according to the pyramid approach in the first year. Arthritis Rheum 2003;48:1797-807.
43. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. Arthritis Rheum 2003;48:1771-4.
44. Mottonen T, Paimela L, Leirisalo-Repo M, Kautiainen H, Ilonen J, Hannonen P. Only high disease activity and positive rheumatoid factor indicate poor prognosis in patients with early rheumatoid arthritis treated with "sawtooth" strategy. Ann Rheum Dis 1998;57:533-9.
45. Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. J Rheumatol 2003;30:1138-46.
46. Young A, Corbett M, Winfield J, et al. A prognostic index for erosive changes in the hands, feet, and cervical spines in early rheumatoid arthritis. Br J Rheumatol 1988;27:94-101.