Disease Progression and Treatment Responses in a Prospective DMARD-naive Seropositive Early Rheumatoid Arthritis Cohort: Does Gender Matter?

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ABSTRACT. ***Objective.*** To assess gender differences in disease characteristics and treatment responses over time in a disease-modifying antirheumatic drug (DMARD)-naive seropositive early rheumatoid arthritis (RA) cohort.

Methods. Patients with polyarticular disease who were DMARD-naive and had seropositive early RA (< 14 months) were recruited by the Western Consortium of Practicing Rheumatologists. Each patient was examined at study entry, after 6 and 12 months, and yearly thereafter. Clinical and demographic data were collected. We investigated gender differences in baseline disease characteristics and treatment using chi-squared, Mann-Whitney U, and t tests. We used generalized estimating equations (GEE) models for repeated measures to examine whether the rate of change of specific disease outcomes during the first 2 years after DMARD initiation was significantly influenced by gender.

Results. At baseline, men (n = 67) and women (n = 225) had similar disease activity and radiographic damage; men, however, had significantly worse erosion, while women had worse joint space narrowing. Despite similar treatment, women had worse disease progression over the 2-year followup, as assessed by trends in Disease Activity Score 28/erythrocyte sedimentation rate (DAS28-ESR4), physician global scores, and tender joint counts. In the GEE model, gender was significantly associated with the rate of change of DAS28-ESR4 scores (p = 0.009), although not independently associated with disease activity. Self-reported measures (Health Assessment Questionnaire-Disability Index, patient global scores, fatigue, pain) were worse among women at baseline and throughout the study period. Men were more likely to achieve remission.

Conclusion. At baseline, men and women had similar disease activity and joint damage. Responses to treatment over time were better among men in this prebiologic era; women had worse progression despite similar treatment. (First Release Oct 1 2010; J Rheumatol 2010;37:2475–85; doi:10.3899/jrheum.091432)

Key Indexing Terms:
RHEUMATOID ARTHRITIS GENDER TREATMENT RESPONSE

Gender differences in rheumatoid arthritis (RA) have been described at multiple levels. Men and women with RA have been found to differ in incidence of the disease[1], extent of disability[2], arthritis-related pain[3], load of genetic risk factors[4,5], and even mortality[6]. Yet the mechanisms by which these differences arise, including the possible involvement of sex hormones[7,8], are as yet unclear. Recently, there has been a renewed interest in gender differences in RA within the rheumatology community, with a focus on disease outcomes and responses to treatment.

Studies of gender differences in disease outcomes and responses to treatment in RA have used a variety of study designs as well as patient populations that vary widely in disease duration and severity, ranging from prospective early RA cohorts[9,10,11] to cross-sectional patient populations with longstanding disease[3,5,12,13]. A number of studies have reported worse RA outcomes among women in terms of symptoms, disease activity, and functional capacity, both in early[14,15] and late RA[3,12,16], although the early RA studies also reported no gender differences in severity in early stages of the disease. In contrast, other studies of longstand-

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ing RA have found men to be more likely to have severity markers, such as higher levels of anti-citrullinated peptide antibodies (ACPA) and the HLA-DRB1 shared epitope[4,5], and to have worse outcomes[13]. It is still unclear whether RA occurs in more severe forms among women or men, and whether the disease progresses differently in each gender. Further, there is now emerging evidence that men may be more likely than women to achieve remission, in response to traditional as well as biologic disease-modifying anti-rheumatic drugs (DMARD)[11,17,18,19]. There is currently much debate about whether the observed differences are intrinsic to the disease. It has been suggested that the gender differences may be accounted for by differences in duration of the disease between men and women[11,20], or may just reflect a gender bias in the reporting of symptoms[12].

Given these conflicting findings and views regarding whether and how men and women with RA differ in their disease characteristics and responses to treatment, detailed examination of prospective early RA cohorts may be better suited to explore these issues, while studies of established RA of variable duration may be limited by their cross-sectional design. Thus, in order to determine whether gender differences, if they do exist, are present in the early stages of the disease or appear in later stages, we have investigated such differences in a prospective DMARD-naive early RA cohort (< 14 months' duration) at baseline[21]; we also examined differences in disease progression and treatment outcomes between men and women in the longitudinal setting, in this fairly homogeneous cohort limited to patients with positive rheumatoid factor (RF) tests and active polyarticular arthritis.

MATERIALS AND METHODS

Patients with RA were recruited between January 1, 1993, and April 1, 2002, as a joint effort of the Western Consortium of Practicing Rheumatologists, through 29 recruitment centers in the western region of the United States and Mexico, including 4 university medical centers, and 25 community practices[21]. To enter the observational study, patients had to (1) satisfy the 1987 American College of Rheumatology (ACR) criteria for RA[22]; (2) be within 14 months of symptom onset; (3) have no prior treatment with a DMARD; (4) have positive titers for rheumatoid factor (RF) antibodies (≥ 40 IU/ml); and (5) have at least 6 swollen joints (of 66) and at least 9 tender joints (of 68).

Approval for the study was obtained from local ethics committees and all participating patients provided informed consent.

Data collection. Each patient was examined by their rheumatologist at the time of entry in the study (baseline), after 6 and 12 months, and yearly thereafter. The rheumatologists collected demographic and clinical data, including joint counts for 68 tender and 66 swollen joints, and physician global assessment at each of these timepoints, as well as data on utilization and outcomes for all DMARD, biologics, and combination therapies used while enrolled in the study. Counts for 28 tender (TJC28) and swollen (SJC28) joints were derived from the recorded 66/68 joint counts. Radiographs of hands/wrists and forefeet were obtained. Patients also completed self-report questionnaires, providing data on their Health Assessment Questionnaire-Disability Index (HAQ-DI), arthritis-related pain on a visual analog scale (VAS), fatigue VAS, and global health and depression scores (Center for Epidemiological Studies Depression Scale, CES-D). Blood samples drawn at baseline and at each followup were used to evaluate levels of RF, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). ACPA titers were measured only at baseline from frozen samples of a subset of subjects at Specialty Laboratories (Valencia, CA, USA).

Assessment of disease activity. Disease Activity Scores (DAS28) using 28-joint counts were computed using (1) ESR:

$$\text{DAS28-ESR4} = [0.56 * \sqrt{(\text{TJC28})} + 0.28 * \sqrt{(\text{SJC28})} + 0.70 * \ln(\text{ESR}) + 0.014 * (\text{global})]$$

and (2) CRP:

$$\text{DAS28-CRP4} = 0.56 * \sqrt{(\text{TJC28})} + 0.28 * \sqrt{(\text{SJC28})} + 0.36 * \ln(\text{CRP} + 1) + 0.014 * (\text{global}) + 0.96$$

Patients were categorized, at baseline, as having mild ($2.6 < \text{DAS28-ESR4} \leq 3.2$), moderate ($3.2 < \text{DAS28-ESR4} \leq 5.1$), or severe ($\text{DAS28-ESR4} > 5.1$) RA disease activity using previously defined criteria based on the DAS28-ESR4[23].

Assessment of radiographs. Radiographs for hands and feet were evaluated for RA joint damage by calculating the erosion and joint space narrowing (JSN) scores using the method developed by Sharp, *et al*[24,25]. Total Sharp scores were calculated by adding erosion scores and JSN scores.

Improvement of RA symptoms and remission. Improvement of disease symptoms was determined based on the ACR criteria for 20% and 50% improvement from baseline[26,27] at 6, 12, and 24 months. We did not use ACR70 criteria because few patients met these criteria. Patients were considered to be in point remission if their DAS28-ESR4 score was < 2.6[28].

Statistical analyses. In a cross-sectional analysis at baseline, differences in disease features and treatment prescribed between men and women were examined, using chi-squared tests to compare distributions of categorical variables; t tests were used for normally distributed continuous variables, and the Mann-Whitney U test for those non-normally distributed. For continuous variables, if normally distributed, means and SD are reported, while medians and 25th and 75th percentiles are reported if non-normally distributed.

In the longitudinal analyses, generalized estimating equations (GEE) models for repeated measures, using an independent correlation structure with robust estimation, were used to model differences in disease activity and disease severity measures as well as frequency of ACR improvement or DAS28 remission between men and women, from baseline to 24 months. For all outcomes examined, followup time and gender were included as the main explanatory variables in the GEE model, adjusting for age, baseline disease activity (DAS28-ESR4), and DMARD prescribed at the baseline visit. An interaction term was also included in the model to evaluate whether the rate of change of the outcome over the 2 years of followup was modified by gender. The GEE model with DAS28-ESR4 as the outcome variable was tested with and without adjusting for RF titers, fatigue VAS, and CES-D scores when evaluating the influence of gender and followup time on disease activity over time. All analyses were repeated in the subset of patients who were prescribed DMARD at the baseline visit, to assess responses to treatment among men and women in terms of the outcomes described. The ESR and CRP variables were analyzed using observed values as well as adjusted values obtained after gender-specific published formulae[29,30] were applied to adjust for age.

In a sensitivity analysis, we assessed gender differences in loss to followup, and repeated the longitudinal analyses in the subset of patients with complete DAS28-ESR4 data at all timepoints.

All statistical analyses were performed using the Stata software package (Release 10, Stata, College Station, TX, USA).

RESULTS

Gender differences at baseline. A total of 292 patients, con-

sisting of 225 women and 67 men with seropositive early RA, were included at baseline. The main gender differences are summarized in Table 1. As expected from the selection criteria, at study entry, all patients had recent-onset RA with a mean duration of 6.2 months (SD 3.5 mo), and men and women had equally active disease, as assessed by the DAS28-ESR4. Overall, the patients had moderate (men 13%, women 15%) or severe disease activity (men 87%, women 84%), with only 1 woman having mild disease activity. Physician global assessment scores were also similar between genders at baseline, as were the total Sharp scores. Compared to women, men had significantly higher erosion scores, swollen joint counts (SJC28), RF titers, and frequencies of nodules; they were also significantly more likely to have ever smoked. Men tended to have later mean age at onset, slightly longer duration of RA symptoms, and were more likely to have radiographic erosions, higher tender joint counts (TJC28), and higher CRP levels and ACPA titers than women, although these differences were not statistically significant. In contrast, women had significantly worse function (HAQ-DI) and significantly higher patient global scores, fatigue, and depression scores (CES-D). They had worse arthritis-related pain and joint space narrowing scores than men, although these were not statistically significant.

Treatment initiated at the baseline visit and first DMARD. Treatment regimens prescribed at the baseline visit are summarized in Table 1. A DMARD [methotrexate (MTX), sulfasalazine, hydroxychloroquine, or gold] was prescribed at the baseline visit for 76% (221 of 292) of patients, i.e., 72%

Table 1. Disease features and medications prescribed at baseline in the cohort of 292 patients with RA, and in men and women separately. In the case of continuous variables, mean values and SD are reported for those variables that were normally distributed; otherwise, medians and interquartile range (IQR) are given. Proportions are shown for categorical variables. P values are also shown for differences derived from Student's t tests, Mann-Whitney U tests, and chi-square tests. Sample sizes denote number of patients for whom data were available for each variable.

Disease Features (Baseline)	Sample Sizes			All Patients	Men	Women	p
	All	Men	Women				
Age at onset, yrs	291	66	225	49.6 ± 13.3	51.3 ± 12.3	49.1 ± 13.6	0.20
Disease duration, mo	292	67	225	6.2 ± 3.5	6.9 ± 3.7	6.1 ± 3.5	0.10
Presence of erosions, % (n)	259	59	200	78.8 (204)	84.8 (50)	77.0 (154)	0.20
Erosion score	259	59	200	0.8 (0.3–2.5)	1.3 (0.5–3.7)	0.7 (0.2–2.0)	0.007
Joint space narrowing score	258	59	199	2.0 (0.5–5.6)	1.8 (0.5–4.3)	2.3 (0.5–5.8)	0.25
Total Sharp score	259	59	200	3.6 (1.3–8.0)	3.6 (1.5–8.8)	3.6 (1.3–8.0)	0.74
Presence of nodules, % (n)	280	64	216	13.9 (39)	21.9 (14)	11.6 (25)	0.04
Tender joint count	279	64	215	13.7 ± 7.5	14.8 ± 7.8	13.4 ± 7.4	0.20
Swollen joint count	279	64	215	13.1 ± 7.1	14.9 ± 6.9	12.6 + 7.1	0.02
CRP, mg/dl	290	67	223	1.4 (0.5–3.4)	1.7 (0.5–3.9)	1.3 (0.5–3.0)	0.40
ESR	290	67	223	37 (23–55)	35 (22–51)	38 (25–55)	0.66
DAS28-ESR4	267	61	206	6.2 ± 1.1	6.3 ± 1.1	6.2 ± 1.2	0.45
DAS28-CRP4	267	61	206	5.1 ± 1.1	5.2 ± 1.1	5.0 ± 1.1	0.48
Physician global VAS	278	64	214	49.2 ± 21.0	49.1 ± 23.2	49.2 ± 20.4	0.99
HAQ-DI score	252	58	194	1.2 ± 0.7	1.0 ± 0.7	1.3 ± 0.7	0.003
Patient global VAS	280	63	217	56.2 ± 27.3	50.0 ± 27.4	58.0 ± 27.1	0.04
Pain VAS	213	44	169	60.4 ± 27.1	53.8 ± 25.9	62.1 ± 27.3	0.07
Fatigue VAS	213	44	169	52.0 ± 24.6	41.4 ± 25.8	54.8 ± 23.6	0.003
CES-D score	217	49	168	13 (7–22)	7 (4–16)	14 (8–23)	0.001
Ever smoked, % (n)	226	55	171	63.3 (143)	83.6 (46)	56.7 (97)	< 0.0005
RF titer (IU/ml), % (n)	281	60	221	211 (88–463)	257 (164–505)	187 (79–459)	0.03
Low titer (12–50 IU/ml)	265	57	208	10.9 (29)	3.5 (2)	13.0 (27)	
Medium titer (51–100 IU/ml)	265	57	208	13.6 (36)	7.0 (4)	15.4 (32)	0.02
High titer (> 100 IU/ml)	265	57	208	75.5 (200)	89.5 (51)	71.6 (149)	
ACPA titer (units/ml), % (n)	123	29	94	249 (129–288)	273 (210–290)	235 (124–284)	0.10
Low titer (20–49 units/ml)	107	25	82	1.9 (2)	0	2.4 (2)	
Medium titer (50–99 units/ml)	107	25	82	7.5 (8)	4.0 (1)	8.5 (7)	0.54
High titer (≥ 100 units/ml)	107	25	82	90.7 (97)	96.0 (24)	89.0 (73)	
DMARD* prescribed at baseline visit, % (n)	292	67	225	75.7 (221)	71.6 (48)	76.9 (173)	0.38
Methotrexate (monotherapy/combination therapy)	292	67	225	49 (143)	46.2 (31)	49.8 (112)	—
Hydroxychloroquine (monotherapy)	292	67	225	15.8 (46)	10.5 (7)	17.3 (39)	—
Sulfasalazine (monotherapy)	292	67	225	7.5 (22)	13.4 (9)	5.8 (13)	—

* Disease-modifying antirheumatic drug: methotrexate, sulfasalazine, hydroxychloroquine, or gold therapy. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Scores using 28-joint counts; VAS: visual analog scale; HAQ-DI: Health Assessment Questionnaire-Disability Index; CES-D: Center for Epidemiologic Studies Depression Scale; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies.

of men and 77% of women (p = 0.38). In terms of first DMARD used for each patient, including those started after the baseline visit, MTX, as monotherapy or in combination with other DMARD, was the first DMARD in 172 patients [37 (55%) men and 135 (60%) women; p = 0.49], which is consistent with expected practice patterns in this prebiologic era.

Changes in disease outcomes over time. Disease activity. During the first 2 years after baseline, mean DAS28-ESR4 scores showed more improvement in men compared to women (Figure 1a). Similar trends were observed for DAS28-CRP4 scores (Figure 1b). In the GEE model, after adjusting for age, RF titers, fatigue VAS, depression score (CES-D), baseline DAS28-ESR4, and baseline DMARD, gender was found to significantly influence the rate of change of the DAS28-ESR4 (p = 0.009), but was not independently associated with this outcome (p = 0.18; Table 2). Significant predictors for DAS28-ESR4 over the 2-year followup included baseline DAS28-ESR4 (p < 0.0005), followup time (p < 0.0005), fatigue VAS (p < 0.0005), RF titer (p = 0.006), and depression score (p = 0.007). As shown in Figure 1c and 1e, tender joint counts and physician global assessment showed similar trajectories to the DAS28-ESR4, with more improvement among men over time. Swollen joint counts, on the other hand, were significantly higher among men at baseline, but were quite similar in both genders thereafter (Figure 1d). Gender was a significant predictor for swollen joint counts (p = 0.03), but not for tender joint counts and physician global scores. Gender did not seem to influence the rate of change of these outcomes (swollen and tender joint counts and physician global scores) over time.

Self-reported measures. Measures of disease activity, functional capacity, and quality of life obtained by patient self-report, i.e., patient global scores, HAQ-DI scores, fatigue VAS, pain VAS, and CES-D scores, were all higher among women at baseline (Table 1). Although they improved in both genders over time, they remained higher among women (Figure 1f, 1g, and 1h; data not shown for pain VAS and CES-D). Accordingly, female gender was significantly associated with these measures in the GEE models where these were the outcome variables. Only pain VAS was not significantly influenced by gender, although it remained higher among women over time. The mean difference, from the GEE models, in each of these measures between women and men was as follows: patient global VAS scores 9.3 (p = 0.001, 95% CI 3.6, 15.0), HAQ-DI 0.30 (p < 0.0005, 95% CI 0.14, 0.46), fatigue VAS 10.2 (p = 0.002, 95% CI 3.9, 16.5), and CES-D scores 4.6 (p = 0.003, 95% CI 1.6, 7.5). However, gender did not influence the rate of change of these self-reported measures during the 2-year followup.

Acute-phase reactants and RF. A different trend was observed for ESR, CRP, and RF. Although levels of these measures decreased significantly in men and women during the first 6 months after baseline, and continued to decrease among men, mean levels among women increased after 6 months (Figure 1j, 1k). However, gender was not significantly associated with these measures (ESR: p = 0.8; CRP: p = 0.8; RF: p = 0.1), or their rate of change. Similar results were obtained for ESR and CRP after gender-specific published formulae were applied to adjust for age.

Radiographic damage. As shown in Figure 2, radiographic damage, as assessed by total Sharp scores, increased significantly over time in both men and women, with mean scores being consistently higher among women. Interestingly, throughout the study period, men had worse erosion scores, and women had worse JSN scores. In the GEE models with JSN scores as outcome, female gender was a significant predictor for higher JSN scores (p = 0.005), but did not influence the rate of change of this outcome. The JSN scores were also significantly influenced by age (p < 0.0005). Interestingly, after stratifying by gender, age was found to be a significant predictor of JSN scores only among women (p < 0.0005), while among men, there was no association with age (p = 0.28).

ACR improvement and DAS28 remission. In the GEE models, gender did not significantly influence ACR20 or ACR50 improvement or DAS28 remission. Nonetheless, there was a nonsignificant trend for increased proportions of men satisfying the criteria for ACR20 improvement and DAS28 remission throughout the 24-month followup, as shown in Figure 3a and 3c. This trend was, however, not observed for ACR50 improvement (Figure 3b).

Responses to treatment. When the analyses were limited to the subset of 221 patients (48 men, 173 women) who were prescribed DMARD at the baseline visit, similar results were obtained as those described, with women showing worse progression and men showing better improvement in the different outcome measures over time (data not shown).

Sensitivity analyses. A total of 15 men and 62 women were lost to followup: 4 men and 19 women were lost to followup by 6 months, 3 men and 13 women by 12 months, 8 men and 30 women by 24 months. Among the patients who remained in the study, data items for random variables were missing for various timepoints in random patients. Repeating the analyses using a subset of 106 patients (26 men and 80 women) who had complete DAS28-ESR4 data from all visits also yielded results similar to those described above for the entire cohort (Figure 4).

DISCUSSION

Our study is the first to report the longitudinal analysis of a prospective DMARD-naive seropositive early RA cohort assessing how gender influences disease activity, functional disability, and radiographic outcomes, as well as subsequent treatment responses, over time, adjusting for within-patient correlation of data[31]. Previous studies examining gender differences in RA have mostly used ordinary linear regression

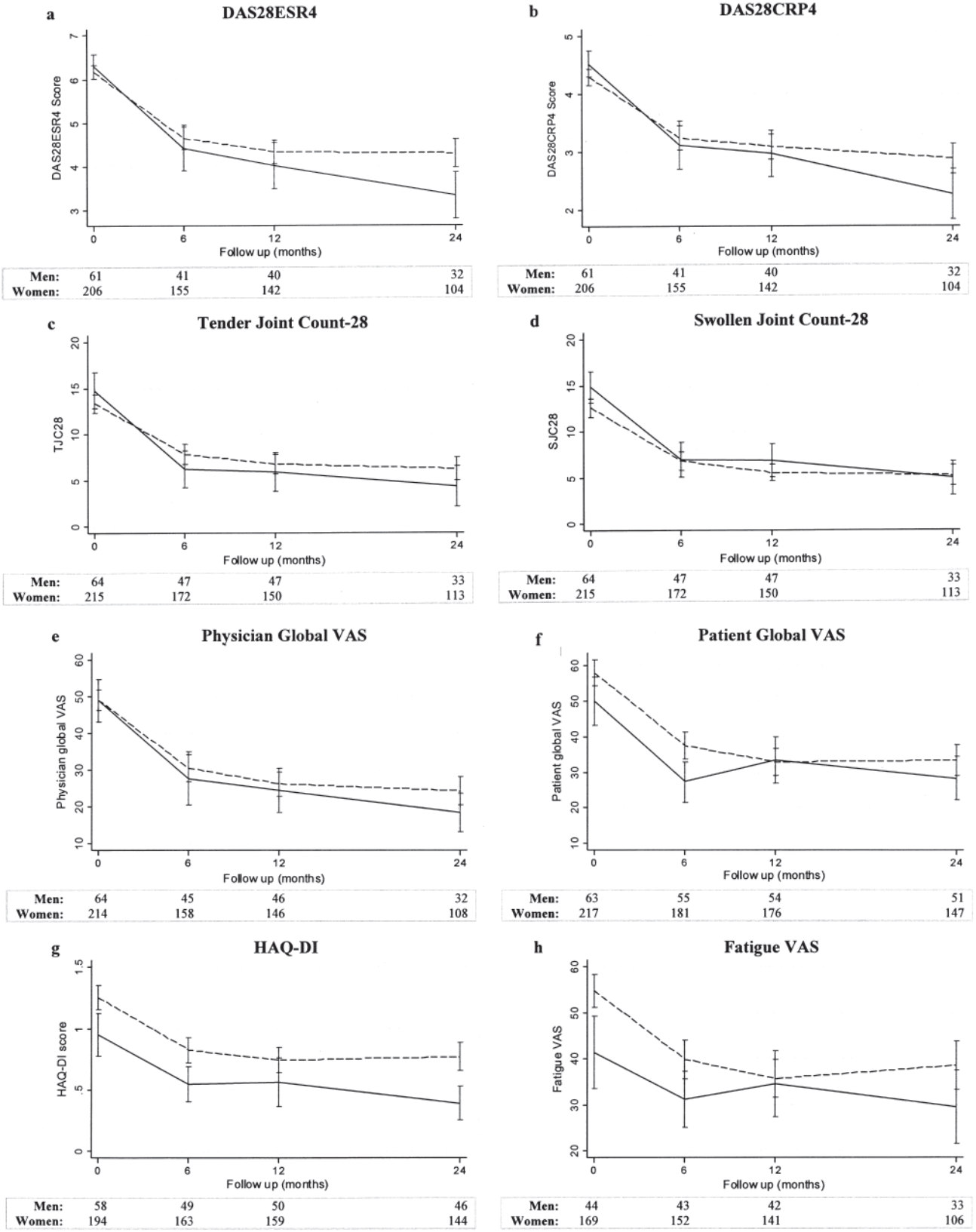


Figure 1. Observed mean values for different outcomes, including the American College of Rheumatology core set measures, in men (solid line) and women (broken line) over the 2-year followup. Bars indicate 95% CI at each point. Numbers of men and women with available data at each timepoint, for each outcome, are shown below each graph (continued overleaf).

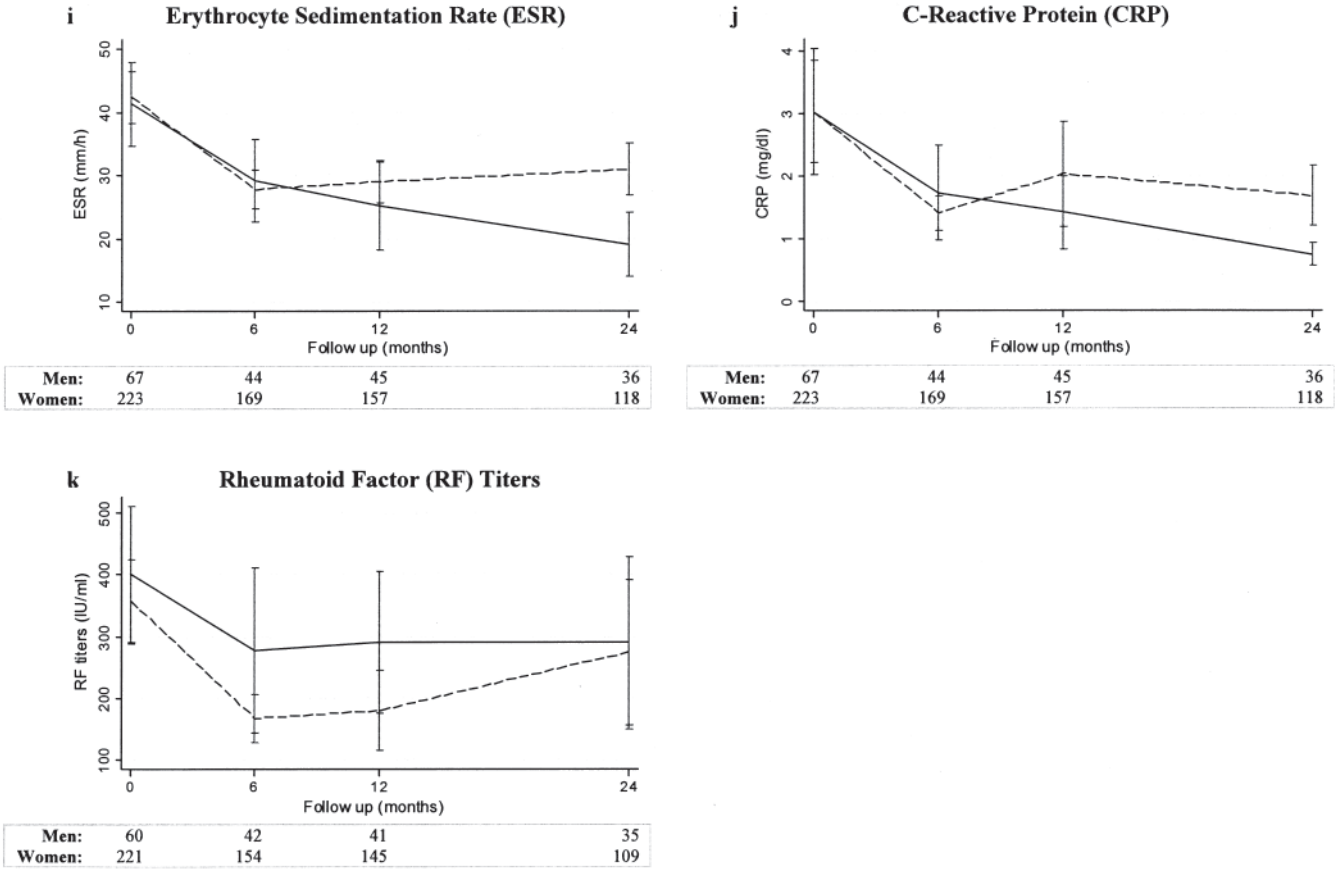


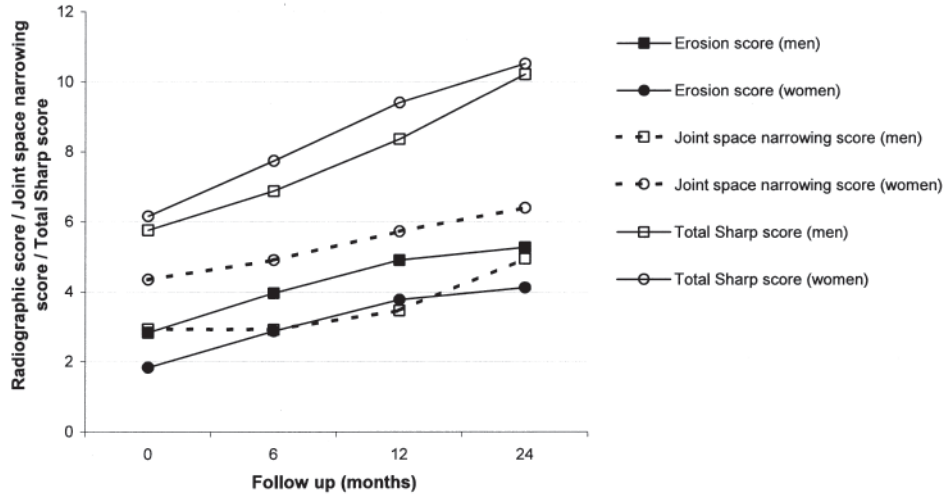
Figure 1. Continued.

Table 2. Longitudinal analysis of predictors of DAS28-ESR4 scores over time using a generalized estimating equations (GEE) model. All covariates adjusted for in the model are listed as independent variables. The referent group for gender was male.

Outcome Variable in GEE Model	Independent Variables	Regression Coefficient (ß) (95% CI)	p
Disease Activity Score (DAS28-ESR4)	Followup time	–0.09 (–0.12, –0.07)	< 0.0005
	Gender	–0.23 (–0.57, 0.11)	0.18
	Gender* followup time (interaction)	0.04 (0.009, 0.06)	0.009
	Age	0.003 (–0.006, 0.01)	0.57
	RF	0.0006 (0.0002, 0.001)	0.006
	Fatigue VAS	0.02 (0.01, 0.02)	< 0.0005
	DAS28-ESR4 at baseline	0.50 (0.39, 0.61)	< 0.0005
	CES-D	0.02 (0.004, 0.03)	0.007
	DMARD prescribed at baseline	–0.20 (–0.54, 0.15)	0.27

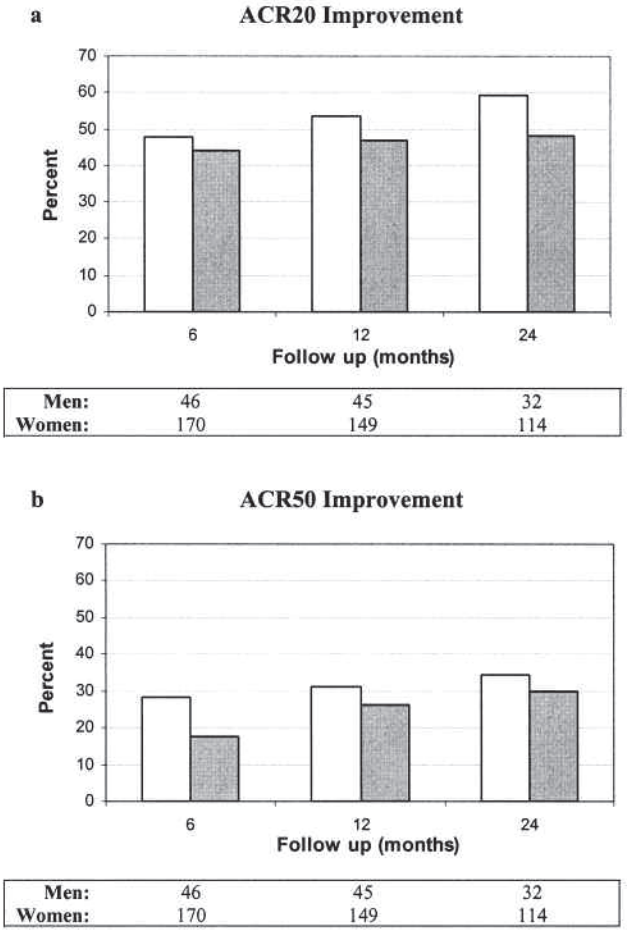
ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Scores using 28-joint counts; VAS: visual analog scale; CES-D: Center for Epidemiologic Studies Depression Scale; RF: rheumatoid factor; DMARD: disease-modifying antirheumatic drug.

and correlation methods to examine the influence of baseline characteristics on disease outcomes after a specified followup time, thus not taking into account within-subject correlation. Our results show that, in this DMARD-naive, seropositive early RA cohort with active polyarticular arthritis, men and women had equally active disease and radiographic joint damage at baseline, although women had higher scores for self-reported measures. Similar proportions of men and women were prescribed DMARD at baseline, or had MTX as their first DMARD during the course of the study. Over time, however, even among patients who initiated DMARD at baseline, disease progression was worse

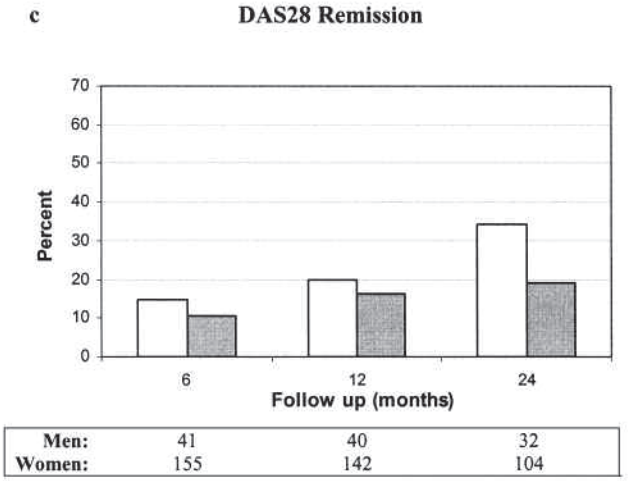


Men:	59	42	38	32
Women:	200	135	121	97

Figure 2. Changes in radiographic damage, assessed by erosion scores, joint space narrowing scores, and total Sharp scores, are shown over the 2-year followup.



Men:	46	45	32
Women:	170	149	114



Men:	41	40	32
Women:	155	142	104

Figure 3. Changes in response to treatment, assessed by ACR20 and ACR50 improvement and DAS28 remission, are shown over the 2-year followup.

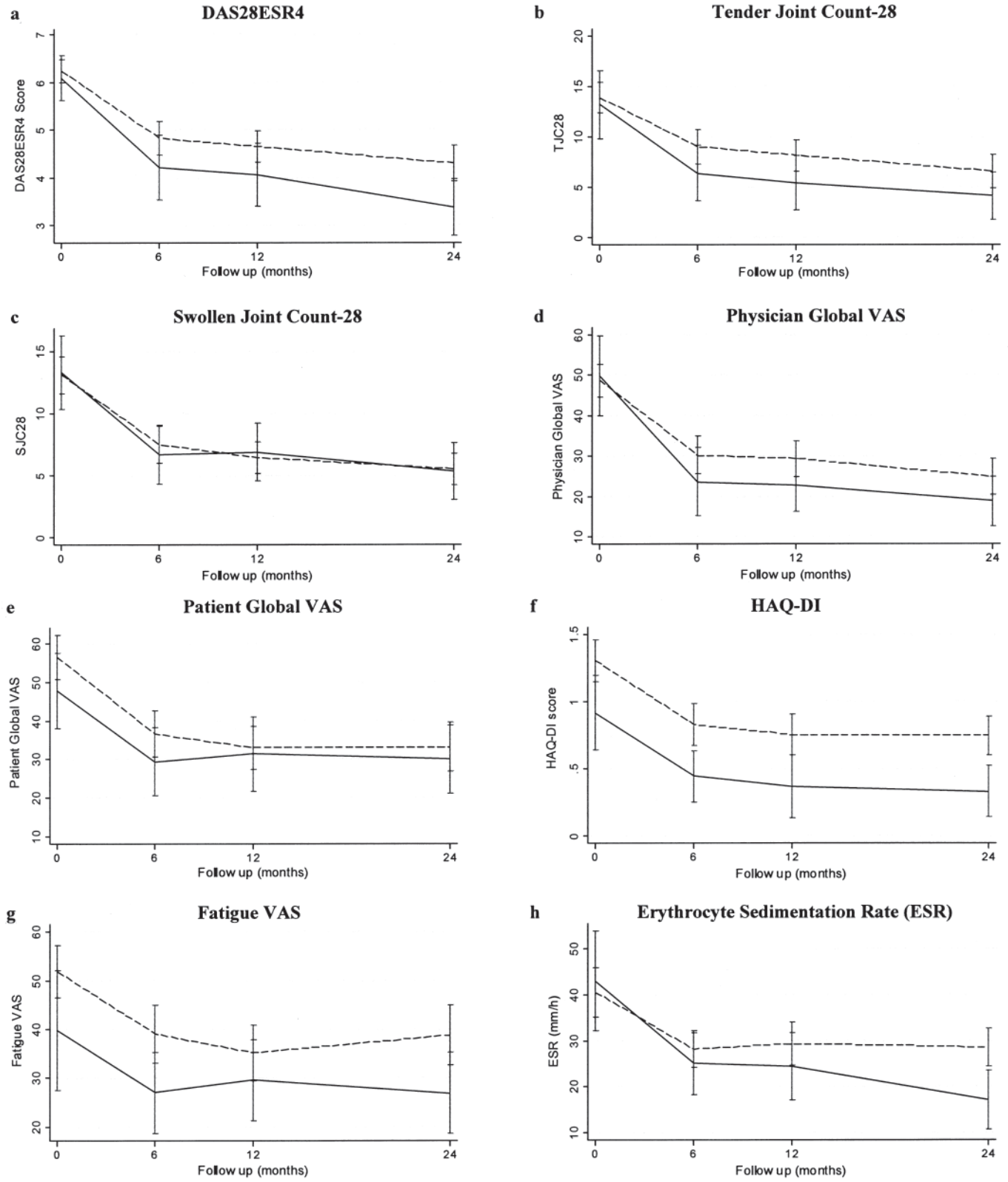


Figure 4. Observed mean values for different outcomes, including the ACR core set measures, for 106 patients (26 men, solid line, and 80 women, broken line) with complete DAS28-ESR4 data at all timepoints over the 2-year followup. Bars indicate 95% CI at each timepoint.

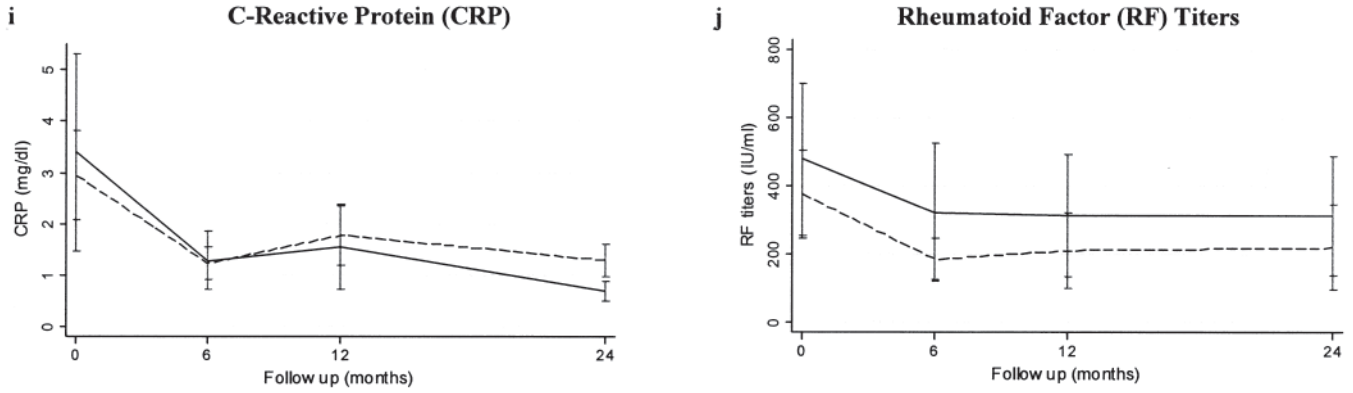


Figure 4. Continued.

among women, while men showed better responses to treatment. Our results are consistent with the existing evidence that, in early stages of the disease, both men and women have similar disease activity, as shown in a cohort in The Netherlands[9], the Swedish BARFOT cohort[10,15], and a cohort in Greece[32], all with RA duration < 12 months at study entry. In contrast, cross-sectional studies of long-standing RA have reported women having more active disease than men[12,17]. This difference is most likely due to different progression rates of RA in men and women. As demonstrated in a number of early RA cohorts[9,14,15], after about 2 years, disease activity tends to be significantly worse among women compared to men, as we also observed. Thus, all currently available evidence points to similar disease activity in the early stages of the disease, followed by a worse disease course among women over time.

It is unclear why women have higher disease activity than men after the disease has progressed for over a year. As seen from the GEE results, in this early RA cohort, the rate of change of disease activity scores was significantly influenced by gender; interestingly, followup time was a significant predictor — a covariate not often taken into account. In examining components of the DAS28-ESR4, it appears that the main differences between men and women were in ESR, with minor differences in tender joint counts and patient global scores. However, even after adjusting the ESR by the standard correction factor for gender and age[29], the reported gender differences in the DAS28-ESR4 at 2 years remained. Further, the trends in improvement of both the DAS28-CRP4 and DAS28-ESR4 scores were significantly better among men in our cohort, suggesting that gender differences in ESR do not explain the observed differences in disease activity, as previously suggested[19]. It has also been argued that observed differences in disease activity are not due to differences in the disease *per se*, but arise as a result of gender differences in reporting of disease activity measures[12,18]. Although the women in our cohort reported worse scores for pain, function, and global health compared to men, this pattern of reporting was consistent throughout the study, including at baseline when there was no gender difference in disease activity. Based on the equation to calculate the DAS28, patient global health scores contribute little to the overall DAS28, while pain VAS and HAQ-DI do not contribute at all, suggesting that differences in these self-reported measures do not account for the increasing difference in disease activity between men and women over time. Further, measures assessed by the physician, i.e., physician global assessment and tender joint counts, also followed the same trends over time as the disease activity scores, with the improvement rates among women starting to slow down after 6 months. Interestingly, an increase in the levels of inflammation markers, i.e., ESR and CRP, as well as in RF levels, was observed among women after 6 months, when disease activity scores started to diverge between men and women. It is possible that women are not as responsive to antiinflammatory medication as men, which might explain the short-lived amelioration in levels of inflammatory markers. This increase in inflammation markers could be related to the increase in tender joint counts and patient global scores, as well as physician global assessment, observed after 6 months, and eventually higher disease activity among women. Increased patient global scores and joint tenderness among women were also observed in the BARFOT cohort and attributed to increased pain perception in women[15]. It is unclear, however, why swollen joint counts were the same in men and women throughout the study duration if there was increased inflammation among women after 6 months.

Given the higher disease activity among women compared to men over time, it not surprising that men appeared more likely to satisfy the ACR criteria for 20% or 50% improvement, and to achieve DAS28 remission in our cohort. This is consistent with previous findings of increased remission among men, both in the early RA cohorts[11,14,18,33] and in well established RA[17,18]. Although most studies have used the less-stringent DAS28 remission criteria, male gender has been significantly associated with remission regardless of the criteria used[18]. In addition to these observational studies, a metaanalysis of data from ran-

domized controlled trials comparing MTX to placebo or other DMARD has also suggested that women were less likely to respond to treatment than men[33].

Interestingly, in our dataset, men and women had similar radiographic joint damage, calculated as total Sharp scores, throughout the study, resulting from higher proportions of men having radiographic erosions and worse mean erosion scores, and women having worse JSN, as reported from other early RA cohorts[9,11,15]. Although the mean JSN scores increased in both men and women over 2 years, age was a significant predictor only among women. It is not clear what other factors are involved among men. It is also unclear why nodules were more prevalent among the men in our study. We and others have previously shown that in longstanding severe RA, men are more prone to nodules[5,13], while other studies found no such gender differences[34]. Since the patients in our early RA cohort were DMARD-naive at study entry, increased nodules in men cannot be explained as a side effect of MTX use, but instead appears to be intrinsic to the disease process. Further, men had higher RF titers than women even though all patients, regardless of gender, had been selected to be seropositive for RF. We had previously reported such a gender bias in RF and ACPA in familial RA[5]. Higher RF titers may be explained in part by the significantly higher proportions of ever-smokers among men, since RF titers appear to be increased among smokers[35]. The ACPA titers among men in this early RA cohort, on the other hand, were only marginally higher than in women, suggesting that the difference we had previously observed[5] could be a feature of familial RA as opposed to sporadic RA.

The study has some limitations. First, the early RA cohort used was clinic-based and was selected for severe RA. It is thus not representative of population-based early inflammatory polyarthritis cohorts. However, men and women were selected using the same criteria; we are not aware of any gender biases in patient selection that may have affected our results. Second, the sample size was small, especially for male patients. Even though the GEE models use all available data, thus increasing the power to detect small associations, the results should be interpreted with caution until replicated in larger early RA datasets. Third, there was some loss to followup and missing data items during the 24-month study period; however, we found no gender biases in the proportions of men and women lost to followup or in the disease activity of those who remained. However, we cannot rule out the possibility of selection bias in the outcome measures of those who were lost to followup. Fourth, we used the DAS28 < 2.6 criterion for remission, which reflects remission at 1 timepoint rather than sustained remission, and is thus less stringent. Since only a few patients satisfied the criteria for ACR remission, we felt that the DAS28 remission was appropriate, and it also allowed our results to be compared with previous reports, most of which have used DAS28 remission. Lastly, the GEE approach does not provide a measure of how well the model fits the data, and hence, the choice of a correlation structure is not always clear. We therefore compared different correlation structures and got similar results.

In summary, based on the results from our cohort, responses to treatment over time in early RA, as assessed by disease outcomes, ACR improvement, and DAS28 remission, appeared to be better among men in the prebiologic era. And although there were no gender differences at baseline in disease activity and radiographic damage, disease progression seemed to be worse among women.

APPENDIX

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