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ORIGINAL ARTICLE

Significance of Sex in Achieving Sustained Remission in the Consortium of Rheumatology Researchers of North America Cohort of Rheumatoid Arthritis Patients

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Objective. **To determine whether men with rheumatoid arthritis (RA) are more likely to achieve remission compared to women.**

Methods. **RA patients enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) cohort between October 2001 and January 2010 were selected for the present analyses. Detailed clinical, demographic, and drug utilization data were available at enrollment (baseline) and at subsequent followup visits. We examined the influence of sex on the Clinical Disease Activity Index remission score (≤2.8) using sustained remission or point remission as the primary outcome measure in multivariate stepwise logistic regression models. We stratified the data by RA duration at baseline (≤2 years or >2 years) to investigate whether RA duration had differential effects on remission in men and women.**

Results. **A total of 10,299 RA patients (2,406 men and 7,893 women) were available for this study. In both early and established RA, women had more severe disease at baseline with worse disease activity measures, modified Health Assessment Questionnaire disability index score, pain on a visual analog scale, and depression. Women were also more likely to have been treated with disease-modifying antirheumatic drugs and anti–tumor necrosis factor therapy compared to men. In the regression models, male sex was associated with sustained remission in early RA (odds ratio [OR] 1.38, 95% confidence interval [95% CI] 1.07–1.78, $P = 0.01$), but not in established RA. However, for point remission, an inverse association was observed with male sex in established RA (OR 0.65, 95% CI 0.48–0.87, $P = 0.005$) and not in early RA.**

Conclusion. **Within the large real-life CORRONA cohort of RA patients, men were more likely to achieve sustained remission compared to women in early RA, although not in established RA.**

INTRODUCTION

With recent advances in available therapies for rheumatoid arthritis (RA) and their effectiveness in management of the disease (1), the goal of RA treatment has evolved from a reduction in pain, despite ongoing inflammation

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Significance & Innovations

- The present study investigates the influence of sex on remission using sustained remission as the outcome of interest, in contrast to previous studies that used point remission.
- This study is the first to report that male sex is a significant predictor for sustained remission in early rheumatoid arthritis (RA), and not in established RA.

and disability, to achievement and sustainability of disease remission (2). However, the ability to respond favorably to treatment and achieve remission varies widely between patients. Over the last few years, there has been a growing interest in a possible role for sex in predicting remission in RA.

A number of studies have reported better responses (3–6) and/or increased remission (4,6–13) among men compared to women in response to both biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs), while some did not find any association between sex and remission (14,15). Thus, although evidence of increased remission among men is accumulating, it has not firmly been established. Further, most of these studies investigated remission at only one point in time, which may not adequately reflect clinical remission.

In the present study, our goal was to examine the role of sex as a potential predictor of remission in a large cohort of patients with RA from the Consortium of Rheumatology Researchers of North America (CORRONA). We wished to test the hypothesis that male sex is a significant predictor of remission in RA.

PATIENTS AND METHODS

Patients. The study population consisted of RA patients enrolled in the prospective observational CORRONA cohort between October 1, 2001 and January 8, 2010. The CORRONA network includes 268 participating academic and community rheumatologists at 103 sites in 35 states within the US. Details of the CORRONA network of recruitment sites and cohort have been published elsewhere (16). All patients who satisfied the 1987 American College of Rheumatology (ACR) criteria for RA (17) and who were being treated by participating rheumatologists were eligible for enrollment into the cohort. Ethical approval for the study was obtained from institutional review boards of participating academic recruitment sites and from a central institutional review board for community-based private recruitment sites. All patients provided written informed consent prior to being enrolled in the cohort.

Data collected. Detailed clinical, demographic, and drug utilization data were collected for each patient at enrollment into the cohort (study baseline) and at subsequent routine followup visits at intervals of ~3 months. The data collected by the participating rheumatologists included joint counts for 28 swollen (SJC28) and tender joints (TJC28), physician global assessment (GA), presence of radiographic erosions, rheumatoid factor (RF) seropositivity, comorbidities, number of previous hospitalizations, and individual components of the ACR response criteria. Drug utilization data were recorded for traditional as well as biologic DMARDs. Patients also completed questionnaires that collected self-reported data on global health assessment (patient GA), pain on a visual analog scale (VAS), work status (full time, part time, not working outside home, student, disabled, or retired), ethnicity, depression prior to baseline, the modified Health Assessment Questionnaire disability index (M-HAQ DI), and use of prednisone and/or anti–tumor necrosis factor (anti-TNF) therapy.

Disease activity scores. Disease activity was assessed as follows: 1) the Disease Activity Score in 28 joints (DAS28) count using 4 variables and the erythrocyte sedimentation rate (ESR) (18) and 2) the Clinical Disease Activity Index (CDAI) scores (19). Disease activity was computed as

$$\text{DAS28} = 0.56(\sqrt{\text{TJC}}) + 0.28(\sqrt{\text{SJC}}) + 0.70 \times \ln(\text{ESR}) + 0.014(\text{GA})$$

$$\text{CDAI} = \text{SJC} + \text{TJC} + \text{physician GA (in cm)} + \text{patient GA (in cm)}$$

CDAI remission as the end point. The primary outcome of interest, i.e., RA remission, was assessed based on CDAI remission (score ≤2.8) (20). Patients were classified as being in "sustained remission" if they were in CDAI remission at any 2 consecutive visits after baseline that were more than 2 months, and up to 6 months, apart. For those patients who did not achieve sustained remission during the study followup, we determined whether they achieved "point remission." Patients were considered to be in point remission if they satisfied the CDAI remission criteria at any single visit after baseline and, for reasons of reliability, if the CDAI score at the remission visit was at least 2.0 units lower than at the previous and subsequent visits. Since patients can often go in and out of remission at different points in time, for each patient who satisfied the point remission criteria in the present study, we chose to include only the first instance of remission.

Statistical analysis. *Baseline sex comparisons.* All patients who had a diagnosis of RA at study baseline were included in the analyses unless they had missing data on sex, ethnicity, and/or CDAI scores at baseline, were in CDAI remission at baseline, or had had a followup of <1 year since enrollment into the cohort. Baseline comparisons of disease characteristics and drug use between men and women were performed using chi-square tests for categorical variables and *t*-tests using a pooled or unpooled SE with Satterthwaite's approximation for degrees of freedom, as appropriate, for continuous variables.

Stepwise multivariate logistic regression. We examined the influence of sex as the main explanatory variable (fe-

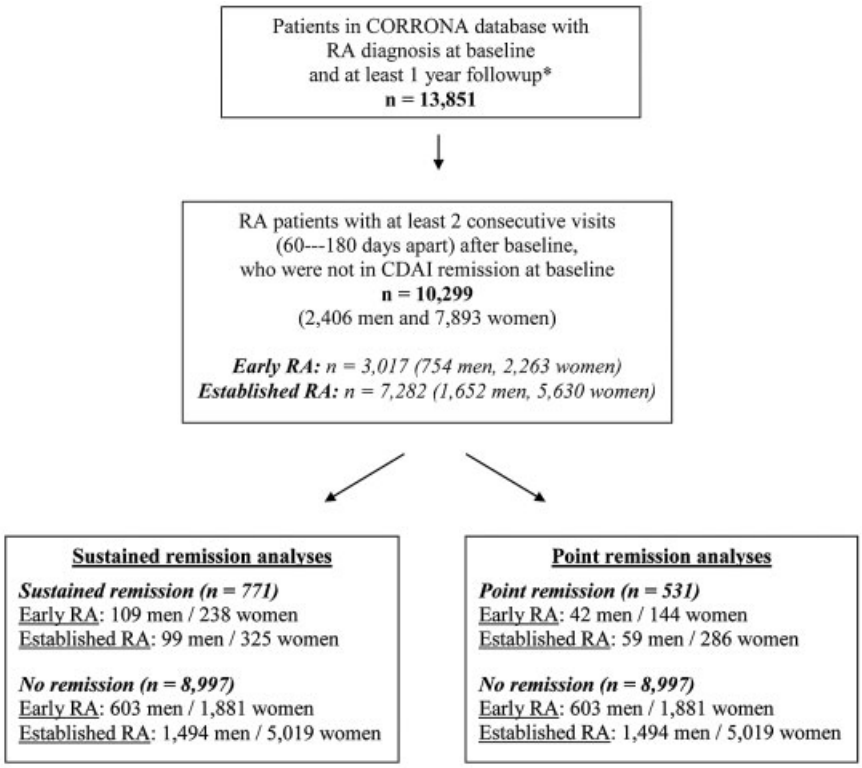

Figure 1. Selection of RA patients from the Consortium of Rheumatology Researchers of North America (CORRONA) database. * = rheumatoid arthritis (RA) patients with nonmissing data for sex, ethnicity, and Clinical Disease Activity Index (CDAI) at baseline.

male sex as the referent category) on CDAI remission using sustained remission as the primary outcome measure in multivariate logistic regression models. Patients who did not attain sustained remission but satisfied our point remission criteria were excluded from these analyses. We also performed a separate analysis for the patients who achieved point but not sustained remission. For both sustained remission and point remission, we used a stepwise regression approach to assess which covariates contributed to the prediction model. Candidate covariates included age, baseline CDAI score, ethnicity (white versus nonwhite, with white as the reference group), RA duration, work status (full time versus part time/not working outside home/student or being disabled/retired, with full time as the reference group), self-reported depression prior to baseline, prednisone use (yes or no), use of anti-TNF therapy (yes or no), strong DMARD use (i.e., methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporine, tacrolimus, gold, etc.), presence of subcutaneous nodules (yes or no), pain on a VAS, and previous hospitalization for RA (yes or no). Since the length of followup varied between patients depending on when they were enrolled in the cohort, and the chances of remission are likely to increase with increasing length of followup, we also adjusted for "length of followup" in the regression models. Further, although we stratified the data according to whether the patients had duration of RA of at most 2 years or more than 2 years, we adjusted for differences in RA duration between patients within the strata.

RESULTS

Baseline comparisons between men and women. A total of 10,299 RA patients (2,406 men and 7,893 women) who were not in remission at baseline were available for the present analyses after we excluded patients who had missing data on sex, ethnicity, or CDAI scores at baseline (Figure 1). The demographic and clinical characteristics of these patients at baseline are summarized by sex and RA duration in Table 1. The patients were predominantly white (>82%). Overall, in both the early RA and established RA groups, the men were older, and a significantly larger proportion of men were married (80% versus 62% [$P < 0.0001$] for early RA and 77% versus 63% [$P < 0.0001$] for established RA) and/or were employed full time (55% versus 44% [$P < 0.0001$] for early RA and 40% versus 32% [$P < 0.0001$] for established RA) compared to women.

Subcutaneous nodules and RF seropositivity were numerically more common among men, whereas radiographic erosions were more common among women; however, these differences were not statistically significant. Disease activity measures were worse among women and included mean ± SD CDAI scores (18.7 ± 13.5 versus 17.4 ± 13.2 [$P = 0.02$] for early RA; 16.6 ± 12.3 versus 15.8 ± 12.0 [$P < 0.0001$] for established RA), mean ± SD tender joint counts (6.1 ± 6.5 versus 4.9 ± 6.0 [$P < 0.0001$] for early RA; 5.0 ± 6.0 versus 4.4 ± 5.6 [$P = 0.0004$] for established RA), mean ± SD ESR (25.6 ± 21.3 mm/hour

Table 1. Disease characteristics at baseline in the CORRONA cohort of RA patients*

Characteristic	Early RA			Established RA		
	Men (n = 754)	Women (n = 2,263)	*P*	Men (n = 1,652)	Women (n = 5,630)	*P*
Age, years	57.9 ± 12.6	53.7 ± 14.2	< 0.0001	60.0 ± 11.8	57.9 ± 12.8	< 0.0001
Disease duration, years	0.9 ± 0.8	0.9 ± 0.8	0.83	12.9 ± 9.1	13.9 ± 9.8	< 0.0001
White race, no. (%)	658 (87.3)	1,868 (82.6)	0.002	1,435 (86.9)	4,654 (82.7)	< 0.0001
Married, no. (%)	596 (79.9)	1,380 (61.5)	< 0.0001	1,266 (77.4)	3,494 (62.8)	< 0.0001
Work status, no. (%)						
Full time	413 (55.1)	987 (43.9)	< 0.0001	657 (40.3)	1,794 (32.2)	< 0.0001
Part time/not working outside home/student	97 (12.9)	673 (30.0)		268 (16.5)	1,627 (29.2)	
Disabled/retired	240 (32.0)	586 (26.1)		704 (43.2)	2,145 (38.5)	
Subcutaneous nodules ever, no. (%)	66 (8.8)	146 (6.5)	0.03	455 (27.6)	1,302 (23.2)	0.0002
Rheumatoid factor seropositivity, no. (%)	351 (73.3)	923 (69.9)	0.16	745 (79.3)	2,305 (77.1)	0.16
Erosions, no. (%)	9 (1.8)	43 (2.8)	0.56	103 (9.3)	427 (10.8)	0.22
ESR, mm/hour	23.5 ± 23.4	25.6 ± 21.3	0.12	20.3 ± 19.6	26.7 ± 22.0	< 0.0001
Tender joint count	4.9 ± 6.0	6.1 ± 6.5	< 0.0001	4.4 ± 5.6	5.0 ± 6.0	0.0004
Swollen joint count	6.3 ± 6.5	6.1 ± 6.2	0.48	5.5 ± 5.7	5.3 ± 5.6	0.31
CDAI	17.4 ± 13.2	18.7 ± 13.5	0.02	15.8 ± 12.0	16.6 ± 12.3	0.02
Morning stiffness, hours	1.6 ± 3.5	1.6 ± 2.9	0.92	1.2 ± 2.3	1.1 ± 1.8	0.29
Physician global VAS	29.5 ± 20.9	31.0 ± 21.0	0.66	26.8 ± 20.2	28.1 ± 20.8	0.02
Patient global VAS	32.6 ± 25.4	35.2 ± 25.9	0.02	32.9 ± 24.5	35.0 ± 25.4	0.005
Patient pain VAS	35.2 ± 26.1	37.8 ± 27.0	0.02	34.1 ± 24.9	36.8 ± 26.0	< 0.0001
M-HAQ	0.36 ± 0.45	0.41 ± 0.45	0.008	0.35 ± 0.43	0.42 ± 0.47	< 0.0001
Self-reported depression, no. (%)	106 (14.3)	594 (27.0)	< 0.0001	255 (15.8)	1,508 (27.6)	< 0.0001
MI or stroke before BL, no. (%)	59 (7.8)	67 (3.0)	< 0.0001	169 (10.2)	205 (3.6)	< 0.0001
Diabetes mellitus before BL, no. (%)	59 (7.8)	142 (6.3)	0.14	160 (9.7)	395 (7.0)	0.0003
Background use, no. (%)						
Prednisone use	289 (38.3)	798 (35.3)	0.13	577 (34.9)	1,782 (31.7)	0.01
TNF inhibitor use	156 (20.7)	589 (26.0)	0.003	819 (49.6)	3,177 (56.4)	< 0.0001
"Strong" DMARD use	457 (60.6)	1,418 (62.7)	0.31	1,064 (64.4)	3,671 (65.2)	0.55
"Weak" DMARD use	65 (8.6)	322 (14.2)	< 0.0001	184 (11.1)	834 (14.8)	0.0002
Previously hospitalized for RA, no. (%)	6 (0.8)	52 (2.3)	0.009	97 (5.9)	294 (5.2)	0.31
Previous joint surgery, no. (%)	183 (24.3)	383 (17.0)	< 0.0001	572 (34.8)	1,945 (34.7)	0.96
Length of followup, quarters	13.7 ± 7.8	13.5 ± 7.9	0.70	16.3 ± 9.0	15.6 ± 8.8	0.009

* Values are the mean ± SD unless indicated otherwise. CORRONA = Consortium of Rheumatology Researchers of North America; RA = rheumatoid arthritis; ESR = erythrocyte sedimentation rate; CDAI = Clinical Disease Activity Index; VAS = visual analog scale; M-HAQ = modified Health Assessment Questionnaire; MI = myocardial infarction; BL = baseline; TNF = tumor necrosis factor; DMARD = disease-modifying antirheumatic drug.

versus 23.5 ± 23.4 mm/hour [$P = 0.12$] for early RA; 26.7 ± 22.0 mm/hour versus 20.3 ± 19.6 mm/hour [$P < 0.0001$] for established RA), and mean ± SD patient global health (35.2 ± 25.9 versus 32.6 ± 25.4 [$P = 0.02$] for early RA; 35.0 ± 25.4 versus 32.9 ± 24.5 [$P = 0.003$] for established RA). Swollen joint counts and morning stiffness were similar between men and women. Mean ± SD physician global scores were higher among women (31.0 ± 21.0 versus 29.5 ± 20.9 [$P = 0.66$] for early RA; 28.1 ± 20.8 versus 26.8 ± 20.2 [$P = 0.02$] for established RA), as were self-reported measures, including the mean ± SD patient pain VAS (37.8 ± 27.0 versus 35.2 ± 26.1 [$P = 0.02$] for early RA; 36.8 ± 26.0 versus 34.1 ± 24.9 [$P < 0.0001$] for established RA), the mean ± SD M-HAQ DI (0.41 ± 0.45 versus 0.36 ± 0.45 [$P = 0.02$] for early RA; 0.42 ± 0.47 versus 0.35 ± 0.43 [$P < 0.0001$] for established RA), as well as self-reported depression prior to baseline (27% versus 14% [$P < 0.0001$] for early RA; 28% versus 16% [$P < 0.0001$] for established RA).

Although in early RA significantly more women had been hospitalized for RA before baseline (0.8% for men versus 2.3% for women; $P = 0.009$), more men had had joint surgery (24% versus 17%; $P < 0.0001$); these differences were not found in established RA. Men and women did not differ in their use of strong DMARDs or prednisone, although in the established RA group more men were using prednisone (35% versus 32%; $P = 0.01$). On the other hand, weak DMARDs (hydroxychloroquine, minocycline) (14% versus 9%; $P < 0.0001$ for early RA and 15% versus 11%; $P = 0.0002$ for established RA) and anti-TNF therapy (26% versus 21%; $P = 0.003$ for early RA and 56% versus 50%; $P < 0.0001$ for established RA) were more commonly used among women. Mean ± SD duration of followup did not differ between men and women (13.7 ± 7.8 versus 13.5 ± 7.9 [$P = 0.50$] for early RA; 16.3 ± 9.0 versus 15.6 ± 8.8 [$P < 0.0001$] for established RA).

Stepwise multivariate logistic regression. *Sustained remission.* A total of 771 patients achieved sustained CDAI remission during the course of the study (Figure 1). In the logistic regression model with CDAI sustained remission as the outcome variable, male sex was a significant predictor of sustained remission in early RA (unadjusted odds ratio [OR] 1.43, 95% confidence interval [95% CI] 1.12–

Table 2. Multivariate logistic regression of sex on sustained CDAI remission*

Variable	Outcome: CDAI sustained remission	
	OR (95% CI)	*P*
RA duration ≤2 years		
Sex†	1.38 (1.07–1.78)	0.01
Ethnicity‡	0.99 (0.71–1.37)	0.96
Baseline CDAI	1.00 (0.99–1.01)	0.65
RA duration	0.75 (0.64–0.89)	0.0007
Depression (self-reported)	0.40 (0.28–0.58)	< 0.0001
TNF inhibitor use	0.65 (0.47–0.89)	0.008
Subcutaneous nodules	0.41 (0.20–0.76)	0.008
Pain VAS	0.99 (0.98–0.99)	< 0.0001
RA duration >2 years		
Sex†	0.93 (0.75–1.22)	0.55
Ethnicity‡	0.91 (0.69–1.20)	0.53
Baseline CDAI	0.99 (0.97–0.99)	0.03
RA duration	0.98 (0.97–1.00)	0.007
Depression	0.71 (0.51–0.86)	0.01
Prednisone use	0.66 (0.50–0.81)	0.0009
Subcutaneous nodules	0.53 (0.42–0.76)	< 0.0001
Pain VAS	0.99 (0.98–0.99)	< 0.0001

* All covariates adjusted for in the final model are listed as independent variables. CDAI = Clinical Disease Activity Index; OR = odds ratio; 95% CI = 95% confidence interval; RA = rheumatoid arthritis; TNF = tumor necrosis factor; VAS = visual analog scale.
† The referent group for this variable was female sex.
‡ The referent group for this variable was white race.

1.82, $P = 0.004$) but not in established RA (unadjusted OR 1.02, 95% CI 0.81–1.29, $P = 0.84$). As shown in Table 2, after adjusting for covariates in the multivariate model, male sex was still associated with an increased odds for sustained remission in early RA (OR 1.38, 95% CI 1.07–1.78, $P = 0.01$), whereas in established RA, no association was observed with sex (OR 0.93, 95% CI 0.72–1.18, $P = 0.55$). In early RA, covariates that were indicative of more severe disease were significantly and inversely associated with sustained remission, i.e., self-reported depression, presence of nodules, use of anti-TNF therapy, and longer RA duration. Ethnicity did not influence remission status.

Table 3. Multivariate logistic regression of sex on CDAI point remission (among those not achieving sustained remission)*

Variable	Outcome: CDAI point remission	
	OR (95% CI)	*P*
RA duration ≤2 years		
Sex†	0.86 (0.59–1.21)	0.39
Ethnicity‡	0.97 (0.62–1.45)	0.88
Baseline CDAI	0.99 (0.98–1.00)	0.06
Prednisone use	1.45 (1.06–1.97)	0.02
RA duration >2 years		
Sex†	0.65 (0.48–0.87)	0.005
Ethnicity‡	0.82 (0.58–1.13)	0.23
Baseline CDAI	0.99 (0.98–1.00)	0.06
Length of followup	1.01 (1.00–1.03)	0.03
RA duration	0.98 (0.97–1.00)	0.01
Pain VAS	0.99 (0.98–0.99)	< 0.0001

* All covariates adjusted for in the final model are listed as independent variables. CDAI = Clinical Disease Activity Index; OR = odds ratio; 95% CI = 95% confidence interval; RA = rheumatoid arthritis; VAS = visual analog scale.
† The referent group for this variable was female sex.
‡ The referent group for this variable was white race.

Point remission (among those not achieving sustained remission). Among the patients who did not achieve sustained remission, 531 achieved point remission. As shown in Table 3 in the stepwise logistic regression model, male sex was inversely associated with point remission among established RA patients (unadjusted OR 0.70, 95% CI 0.52–0.92, $P = 0.01$), but not in the early RA group (unadjusted OR 0.88, 95% CI 0.61–1.24, $P = 0.48$). After adjusting for covariates, male sex was still inversely associated with point remission in established RA (OR 0.65, 95% CI 0.48–0.87, $P = 0.005$), but not early RA (OR 0.85, 95% CI 0.59–1.21, $P = 0.39$).

DISCUSSION

In this large observational cohort of RA patients from the CORRONA database, male sex was a significant and independent predictor for sustained CDAI remission. This association was seen in early RA and was not observed in established RA. Since there were a number of variables associated with sex at baseline in this cohort, such that women had more severe baseline disease, we identified among them those that we believed could potentially influence remission and adjusted for them in the logistic regression models. These included baseline CDAI scores, anti-TNF therapy, self-reported depression, pain on a VAS, and the work status category (included as patients who worked part time, did not work outside the home, or were students). Adjusting for these confounders in the logistic regression models slightly reduced the strength of the association. Nonetheless, male sex remained significantly and independently associated with sustained remission in the early RA group. Thus, although the contribution of sex was relatively small, it is most likely real and not just a statistical artifact. Further, the smaller numbers of men compared to women in our analyses do not, in our opinion, change the results as they, in fact, represent a relatively large sample of men for RA studies. Among the patients who did not achieve sustained remission during our study followup of this CORRONA cohort, sex did not influence point remission in early RA, although women were more likely to achieve point remission than men in the established RA group.

The present study is the first to report that male sex is a significant predictor for sustained remission in early RA in contrast to established RA. Most previous studies on this topic had examined the influence of sex on point remission in RA (7,9,11–13,21). However, point remission may be limited in its clinical importance as it is based on data from a single time point and may not be as reliable or clinically relevant as sustained remission, which is based on data from at least 2 time points spread over a period of time. An association with sustained remission had been

reported in an early RA cohort (8), but similar investigations in established RA cohorts had not been performed. Despite variations in the definitions of remission used in the different studies based on the DAS44, DAS28, simplified DAI, CDAI, and ACR criteria (13), our findings are in agreement with previous reports of male sex being a significant predictor of remission in RA (4,6–13). We also previously examined response measures other than remission in men and women with RA, including European League Against Rheumatism (EULAR) responses in 2 other RA cohorts (5,22), and found that men had better EULAR responses compared to women in early RA and not established RA (22). Thus, our findings of increased sustained remission among men in early RA and not established RA in the CORRONA cohort are in agreement with those previous findings and support the finding that men have better responses irrespective of the treatment outcome under study, including sustained remission.

In general, sex-specific investigations as presented here have not been addressed in most studies of RA remission. Among the few studies that have examined sex as a predictor for remission, either as a primary predictor or as a covariate in the multivariate analyses, only 2 did not find an association between sex and remission (14,15). This could be due to the very small sample sizes (195 and 105 patients, respectively) in both of these studies. In the large multinational Quantitative Patient Questionnaires in Standard Monitoring of Patients with RA study, although it was shown that men achieved remission more often than women irrespective of the definition of remission (13), it has also been postulated that sex differences in RA disease activity may be the result of a sex bias in reporting of disease activity measures (21). One could also speculate other possibilities to explain the data, including immunologic response differences, drug dosing differences, and genetic differences between men and women. Our data do not allow us to differentiate among these possibilities.

It is as yet unclear why men are more likely than women to achieve sustained remission in early RA and not established RA. As we and others have demonstrated, patients with shorter RA duration, i.e., early RA, are more likely to achieve remission (3,23). It is therefore quite plausible that treatment responses and rates of remission may be of a smaller magnitude among both men and women in established RA, thus making the sex differences less apparent, especially since the difference in response observed between men and women in early RA is in itself relatively small. The increased odds of sustained remission among men in early RA is nevertheless intriguing and has not yet been explained. Presumably, such differences in treatment response between men and women could arise as a result of genetic, physiologic, immunologic, or even psychosocial differences between the sexes. In the multivariate regression models, self-reported depression, subcutaneous nodules, and anti-TNF therapy were significant predictors for no remission. It may be expected that more severe disease, as indicated by subcutaneous nodules and anti-TNF therapy, and being depressed would reduce the probability of remission as suggested from previous studies (24–26). Even after these confounders were adjusted in the logistic regression models, male sex was still a significant and independent predictor of sustained remission in the CORRONA cohort. Furthermore, there were no differences between men and women in the effect of self-reported depression, anti-TNF therapy, or prednisone on sustained remission in the CORRONA cohort (data not shown). This suggests that there are additional sex-specific factors in operation in influencing the chances of sustained remission in RA, especially in the first two years after diagnosis. The range of possible physiologic, immunologic, and psychological factors that may differ between men and women and that could influence remission in RA is vast, and identification of the specific culprit responsible for the increased sustained remission among men in early RA is beyond the scope of this study.

There may also be "gender" differences contributing to men being more likely to undergo sustained remission. For example, CDAI scores, and hence CDAI remission, are highly dependent on pain perception. We could speculate that men may have a higher threshold for reporting joint tenderness and global health in the early stages of the disease, but as disease duration increases, adaptive mechanisms relating to pain perception may be in operation, leading to more similar reporting of symptoms between men and women. Regarding patients who did not achieve sustained remission, however, we cannot explain our findings of why women should be more likely to achieve point remission in established RA and not in early RA.

The large number of sites, relatively long followup, both physician-derived and patient-derived outcomes, and use of a "real-life" cohort represent significant strengths of the study. There are also some limitations in this study. Our results demonstrate an association between male sex and sustained remission in early RA; however, the available data and observational nature of the CORRONA cohort do not allow us to determine the cause of this association. Although our database size allows us to adjust for many potential confounders, the possibility remains that there may be additional unknown confounders that we have not recorded and so could not adjust for in the multivariate models, including the true causative agent. We used CDAI remission as our outcome measure because data on the CDAI were available on a larger number of patients in the CORRONA database and because CDAI remission is a more rigorous definition of remission. Although there is currently no gold standard for assessing clinical remission in RA, comparisons of measures of remission have shown that the CDAI remission criteria are more stringent than those for DAS28 or modified ACR remission, allowing for less residual disease activity (27). Therefore, we feel that the CDAI remission is an appropriate measure for the primary outcome in this study.

Given the large sample size of the CORRONA cohort, it is possible that statistical significance may have been achieved as a result of the large sample size without reflecting clinical significance, as seen for some of the baseline comparisons in Table 1. Our main finding that men are more likely to achieve sustained remission does not, however, appear to be the result of a statistical artifact. Nonetheless, we would like to point out that the number of men in our study cohort, although large for RA studies, is not large enough to make the results irrefutable. The data

analyzed in the present study were collected at over 100 different sites by different rheumatologists who are part of the CORRONA network. Some subtle variation in the clinical measures recorded may have been introduced as a result of assessment by different rheumatologists, or there may have been differences in routine clinical care and standard treatment practices specific to certain recruitment sites. At the same time, that same large number of sites and physicians mitigates against a systematic difference in these areas. The CORRONA cohort consists of patients in routine clinical care enrolled since 2001, and the inclusion criteria only required that the patients satisfy the 1987 ACR criteria for RA and were being treated by a rheumatologist participating in the CORRONA network. Therefore, within the cohort, patients had variable RA duration and had been on various therapies for various lengths of time. We could not adjust for duration of therapy in the analyses presented as we did not have accurate data on drug usage before cohort enrollment. As a proxy for treatment duration, we adjusted for RA duration under the assumption that treatment started soon after diagnosis.

In summary, within the large real-life CORRONA cohort of RA patients, men were more likely to achieve sustained remission compared to women in early RA, although not in established RA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Furst had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Jawaheer, Messing, Reed, Kremer, Louie, Furst.

Acquisition of data. Messing, Kremer, Louie, Furst.

Analysis and interpretation of data. Jawaheer, Messing, Ranganath, Louie, Khanna, Greenberg, Furst.

ROLE OF THE STUDY SPONSOR

Abbott, Amgen, BMS, Centocor, Genentech, Lilly, and Roche had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Abbott, Amgen, BMS, Centocor, Genentech, Lilly, or Roche.

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