The Journal of Rheumatology 2022;49:990–7
doi:10.3899/jrheum.211199
First Release July 1 2022

The Journal of Rheumatology

Male Sex Predicts a Favorable Outcome in Early ACPA-Negative Rheumatoid Arthritis: Data From an Observational Study

Giovanni Cagnotto[1], Lennart T.H. Jacobsson[2], Emil Rydell[3], Anna Eberhard[1], Michele Compagno[1], and Carl Turesson[1]

ABSTRACT. ***Objective.*** The aim of the present study was to investigate whether the relationship between sex and clinical outcomes in early rheumatoid arthritis (RA) varies by autoantibody status.

Methods. Two inception cohorts of consecutive patients with early RA (ie, symptom duration ≤ 12 months) in the southern region of Sweden were investigated. Patients were stratified by anticitrullinated peptide antibody (ACPA) status. The primary outcome was remission (Disease Activity Score in 28 joints [DAS28] < 2.6) at 12 months. Secondary outcomes were remission at 6 months and European Alliance of Associations for Rheumatology good response at 6 and 12 months compared to baseline. In logistic regression models, which were adjusted for age, DAS28 values, and Health Assessment Questionnaire values at baseline, the relationship between sex and clinical outcomes, stratified by ACPA status, was investigated.

Results. In total, 426 patients with early RA were included: 160 patients were ACPA negative and 266 patients were ACPA positive. At 12 months, 27.1% (38/140) of females and 24.1% (13/54) of males with ACPA-positive RA achieved DAS28 remission. In ACPA-negative RA, 16.0% (13/81) of females and 48.6% (18/37) of males achieved DAS28 remission at 12 months. Males had higher odds of reaching remission at 12 months in the ACPA-negative patient group (pooled adjusted odds ratio [OR] 4.79, 95% CI 1.97-11.6), but not in the ACPA-positive group (pooled adjusted OR 1.06, 95% CI 0.49-2.30).

Conclusion. Male sex was associated with better clinical outcomes in ACPA-negative early RA, but not in ACPA-positive early RA. The poor outcomes in females with early seronegative RA suggest that this represents a difficult-to-treat patient group.

Key Indexing Terms: outcomes, rheumatoid arthritis, sex

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a prevalence of approximately 0.5% worldwide.[1] If left untreated, it leads to progressive destruction of cartilage and bone, causing impaired physical function, as well as increased mortality.[2,3] The prognosis of patients with RA has improved in the last few years, as a result of earlier and more intensive treatment strategies and the development of several effective drugs with favorable safety profiles.[4] However, a substantial proportion of patients still have unsatisfactory treatment responses and need to try multiple drugs to achieve the desired outcomes.[5] Investigators have tried to find predictors of treatment outcomes that could help clinicians to choose the most appropriate drug for each patient, but the results have been inconclusive or inconsistent so far.[6-12] Anticitrullinated peptide antibodies (ACPA), usually analyzed as anticyclic citrullinated peptide (anti-CCP) antibodies, are used as both diagnostic and prognostic markers of RA. The presence of ACPA is associated with greater progression of joint damage and worse prognosis in patients with RA.[13] Indeed, ACPA-positive RA is the most studied phenotype of RA, and the majority of patients with RA included in randomized clinical trials are ACPA positive. On the other hand, there is less information on ACPA-negative RA. This RA phenotype is thought to be associated with a more favorable disease course. However, results on the predictive value of ACPA on clinical outcomes are controversial.[14] We have previously demonstrated that although ACPA positivity predicts rapid radiographic progression,[15] unacceptable levels of pain despite low inflammation are more common in ACPA-negative RA.[16]

Incidence of RA is higher in women than in men,[1] and sex hormones have been implicated in the pathophysiology of the disease.[17] Yet, data on the role of sex as a predictor of outcomes in RA are also conflicting.[10,18,19] To our knowledge, no previous

This work was supported by the Swedish Research Council (grant no. 2015-02228), the Swedish Rheumatism Association (grant no. R-664091), and Lund University (grant no. ALFSKANE-446501).

[1]G. Cagnotto, MD, Senior Consultant Rheumatologist, A. Eberhard, MD, M. Compagno, MD, PhD, Senior Consultant Rheumatologist, C. Turesson, MD, PhD, Professor, Rheumatology, Department of Clinical Sciences, Lund University, and Department of Rheumatology, Skåne University Hospital, Malmö; [2]L.T.H. Jacobsson, MD, PhD, Professor, Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, Gothenburg University, Gothenburg; [3]E. Rydell, MD, Rheumatology, Department of Clinical Sciences, Lund University, Malmö, Sweden.

LTHJ reports lecture and consulting fees from Novartis, Eli Lilly, and Janssen. MC reports consulting fees from AbbVie and Sanofi Aventis. CT reports consulting fees from Roche; speaking fees from AbbVie, BMS, Nordic Drugs, Pfizer, and Roche; and an unrestricted grant from BMS. The remaining authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. G. Cagnotto, Reumatologimottagning, Jan Waldenströms gata 1b, Malmö 20502, Sweden.
Email: Giovanni.cagnotto@med.lu.se.

Accepted for publication April 20, 2022.

studies have investigated the relationship between sex and clinical outcomes in RA separately by ACPA status. Therefore, the present study aimed to analyze the predictive value of sex for clinical outcomes in patients with ACPA-positive and ACPA-negative early RA.

METHODS

Patients with early RA. This was an observational cohort study investigating patients with early RA from southern Sweden. Two cohorts of consecutive patients with early RA were investigated. Cohort I was an inception cohort of patients with early RA (ie, symptom duration ≤ 12 months); these patients were recruited from 1995 to 2005.[15,20] The patients were diagnosed with RA by a rheumatologist and fulfilled the 1987 revised American College of Rheumatology (ACR) classification criteria for RA.[21] The ACR/European Alliance of Associations for Rheumatology (EULAR) 2010 classification criteria for RA[22] were fulfilled by at least 88% of the patients.[16] The cohort included individuals from a defined area, the city of Malmö, Sweden, with a population of 260,000 in 2000. Patients were recruited from the rheumatology outpatient clinic of Malmö University Hospital, which was the only hospital serving the city, and from the 4 rheumatologists in private practice in Malmö. Patients were followed according to a structured program as previously described.[16] Disease activity was measured by the Disease Activity Score in 28 joints (DAS28),[23] and disability was evaluated using the Swedish validated version of the Health Assessment Questionnaire (HAQ).[24] The number of swollen and tender joints (out of 28) was assessed by the same rheumatologist in all patients at all visits. At inclusion, all patients were tested for rheumatoid factor (RF) and anti-CCP seropositivity, using standard ELISA methods at the immunology laboratories of the university hospitals in Malmö and Lund. IgM RF was analyzed using ELISA, which was calibrated against the World Health Organization RF reference preparation. Anti-CCP antibodies were analyzed using the QUANTA Lite anti-CCP2 IgG ELISA (Inova Diagnostics). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were assessed according to standard methods at the Department of Clinical Chemistry, Malmö University Hospital. During part of the study period, high-sensitivity CRP analysis was not available, and CRP values between 0 and 9 mg/L were reported by the laboratory as < 9 mg/L.

Cohort II consisted of patients with early RA (ie, ≤ 12 months of symptom duration), according to the 1987 revised ACR criteria[21] or the 2010 ACR/EULAR classification criteria for RA.[22] This cohort consisted of patients who had been diagnosed and followed at the outpatient rheumatology clinic of Skåne University Hospital from 2012 to 2016 and who were included in the Swedish Rheumatology Quality Register (SRQ).[25] The SRQ is a nationwide Swedish clinical register of patients with chronic inflammatory joint diseases, including RA.[25] The SRQ includes clinical information on disease characteristics, including the DAS28 and the HAQ, and antirheumatic treatment, prospectively recorded at treatment initiation and at subsequent visits. Dates of starting and stopping treatment and the cause of discontinuing treatment are recorded by the physician who manages the patient at each visit, as part of regular clinical care. Data on ACPA status and RF were retrieved from the clinical records. During the study period, ACPA levels were assessed using standard ELISA methods for anti-CCP2 at the immunology laboratories of Skåne University Hospital, and IgM RF levels were analyzed using ELISA, as described above. ESR and high-sensitivity CRP levels were assessed according to standard methods at the Department of Clinical Chemistry, Skåne University Hospital. The Clinical Disease Activity Index (CDAI) was estimated post hoc in patients of both cohorts. Physician global assessment of disease activity was originally measured as a 5-grade ordinal Likert scale (0-4) for most of the patients. The measures were translated into a 10-cm visual analog scale (VAS) suitable for calculating CDAI using the following method, based on a limited number of patients with both Likert scale and VAS data available: values of 0 in the Likert scale were reported as 0.5 cm in the new VAS, and values of 1 corresponded to 2.0 cm, 2 to 4.0 cm, 3 to 7.0 cm, and 4 to 9.0 cm.

Follow-up and clinical outcomes. In cohort I, patients were followed with scheduled visits at 6 and 12 months after inclusion. Clinical characteristics were collected at follow-up according to a prespecified protocol. Follow-up data of patients in cohort II were retrieved from visits registered in the SRQ. The 6-month and 12-month follow-ups were represented by data from visits closest to 6 and 12 months from inclusion within time windows of 5 to 8 months and 10 to 15 months, respectively. Missing data from the SRQ were retrieved by review of electronic medical records, when possible. Patients in both cohorts were treated according to standard care.

The primary outcome was the proportion of patients with ACPA-negative and ACPA-positive RA achieving clinical remission[26] (DAS28 < 2.6) at 12 months. Secondary outcomes were the proportions of these patients achieving DAS28 remission at 6 months or a EULAR good response[27] at 6 and 12 months compared to baseline. The proportions of patients achieving CDAI remission (≤ 2.8) at 6 and 12 months were assessed as exploratory outcomes.

Statement of ethics and consent. The study was approved by the Regional Ethical Review Board for southern Sweden (Lund, Sweden: LU 410-94) and was conducted in accordance with the Declaration of Helsinki. All participants gave their written informed consent to participate in the study.

Statistics. In both cohorts, only patients with available DAS28 data at baseline were included in the analyses. Baseline features among females and males, stratified by ACPA status, were compared using the chi-square test, the Mann-Whitney *U* test, or the independent-samples *t* test, as appropriate. Proportions of females and males achieving outcomes, stratified by ACPA status, were compared using the chi-square test.

The predictive value of sex for primary, secondary, and exploratory outcomes was investigated by means of logistic regression models, using the chosen outcomes as dependent variables and sex as the covariate. The odds ratio (OR) for each outcome was estimated, and a 95% CI was calculated. Analyses were stratified by ACPA status and presented separately for patients who were ACPA positive and ACPA negative. We also added a nonstratified model with an interaction term (ie, sex × ACPA status) to determine whether ACPA status acted as an effect modifier on the association between sex and clinical outcomes. As baseline DAS28 values influence the chance of achieving remission or a EULAR good response, all analyses were adjusted for DAS28 at baseline. As high HAQ values are established negative predictors of treatment response,[28-30] all models were also adjusted for baseline HAQ values. Further, adjustment for age was also performed, since younger patients with early RA seem to have a better clinical outcome.[31]

Analyses were performed for each cohort and after pooling cohort I and cohort II data. Statistical analysis was performed using SPSS Statistics (version 26; IBM Corp).

RESULTS

Baseline characteristics in cohort I. A total of 233 patients were evaluated, of which 225 had DAS28 data at baseline. Of these, 130 patients (92 females and 38 males) were ACPA positive and 95 (66 females and 29 males) were ACPA negative. Demographic and clinical disease characteristics at baseline were comparable between patients who were ACPA negative and ACPA positive, as well as between men and women in each ACPA subgroup (Table 1). However, there were some minor differences in the number of swollen and tender joints between females and males in the ACPA-negative group ($P < 0.05$).

Baseline characteristics in cohort II. A total of 283 patients fulfilled the criteria for inclusion in cohort II, of which 201 had available DAS28 data at baseline. Of these, 136 patients (105 females and 31 males) were ACPA positive and 65 (41 females and 24

Table 1. Baseline characteristics of cohort I and cohort II.

	Cohort I				Cohort II			
	ACPA Positive, n = 130		ACPA Negative, n = 95		ACPA Positive, n = 136		ACPA Negative, n = 65	
	Females	Males	Females	Males	Females	Males	Females	Males
Patients, n (%)	92 (70.8)	38 (29.2)	66 (69.5)	29 (30.5)	105 (77.2)	31 (22.8)	41 (63.1)	24 (36.9)
Age, yrs	62 (50-70)	63 (57-70)	61 (46-75)	67 (54-74)	57 (42-69)	64 (57-70)	68 (52-72)	67 (56-71)
Duration, months	8 (5-10)	7 (5-10)	7 (5-10)	7 (4-10)	5 (3-7)	6 (3-7)	6 (4-9)	4 (3-6)
RF positive, n (%)	71 (77.2)	34 (89.5)	21 (31.8)	11 (37.9)	87 (82.9)	22 (71.0)	19 (46.3)	6 (25)
DAS28, mean (SD)	4.6 (1.40)	4.8 (1.46)	4.7 (1.28)	4.3 (1.55)	4.9 (1.50)	5.0 (1.51)	5.2 (1.48)	4.8 (1.86)
HAQ	0.75 (0.38-1.25)	0.75 (0.13-1.13)	0.88 (0.5-1.38)	0.63 (0.19-1.06)	1.0 (0.5-1.38)	0.94 (0.38-1.28)	1.13 (0.5-1.72)	1.0 (0.75-1.47)
CRP, mg/L	9.5 (0-26.7)	13.5 (0-34.2)	0 (0-14.2)	5 (0-28.5)	6.3 (2.1-22.7)	18 (3.8-42)*	8.6 (3.8-25.7)	13.5 (8.6-37)
ESR, mm/h	24 (14-50)	28 (13-53)	17 (9-30)	20 (10-34)	25 (13-47)	33 (17-58)	31 (13-52)	26 (13-48)
SJC28	7 (4-9)	7 (5-12)	6 (4-11)	8 (7-12)*	4 (2-8)	6 (3-10)	6 (3-11)	9 (2-13)
TJC28	4 (1-7)	3 (1-9)	7 (3-13)	2 (0-7)*	6 (2-10)	6 (3-9)	8 (4-11)	5 (2-13)
Methotrexate, n (%)	48 (52.2)	19 (50)	41 (62.1)	17 (58.6)	76 (72.4)	17 (54.8)	28 (68.3)	17 (70.8)
bDMARDs, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	11 (10.5)	8 (25.8)*	4 (9.8)	1 (4.2)

Data are in median (IQR) unless otherwise indicated. * $P < 0.05$ vs female patients. ACPA: anticitrullinated peptide antibody; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; SJC28: swollen joint count in 28 joints; TJC28: tender joint count in 28 joints.

males) were ACPA negative. Disease characteristics at baseline were similar between patients who were ACPA positive and ACPA negative and between females and males in each ACPA subgroup (Table 1). There were differences in CRP levels at baseline as well as in the proportion of patients on biologic (b-) disease-modifying antirheumatic drugs (DMARDs) between female and male patients who were ACPA positive ($P < 0.05$). However, treatment regimens were similar in male and female patients at 12 months (Supplementary Table S1, available with the online version of this article).

Baseline characteristics in the pooled cohort. A total of 426 patients were included in the pooled cohort (Table 2). Demographic and baseline characteristics were similar in the ACPA-positive and ACPA-negative groups, and in most cases, they were similar between females and males in the 2 ACPA subgroups. However, in the ACPA-positive subset, men were older and had higher CRP levels and swollen joint counts, and in the ACPA-negative subset they had shorter disease duration and lower tender joint counts ($P < 0.05$; Table 2). Importantly, there were no significant differences in treatment regimen between females and males during the follow-up (Table 2; Supplementary Table S1, available with the online version of this article).

Outcomes. In the pooled cohort, 26.3% (51/194) of patients who were ACPA positive and 26.3% (31/118) of patients who were ACPA negative achieved DAS28 remission at 12 months. A higher proportion of male patients were in remission at 6 and 12 months as compared to female patients in the ACPA-negative subset; males also had a higher likelihood of a major treatment response than females at 12 months (Table 3). Sex-related differences in outcomes were not observed in the ACPA-positive subset (Table 3). Similar results were observed when using CDAI remission as the outcome (Supplementary Table S2, available

Table 2. Baseline characteristics of the pooled cohort.

	Pooled Cohort, N = 426		ACPA Positive, n = 266		ACPA Negative, n = 160	
	Females	Males	Females	Males	Females	Males
Patients, n (%)	304 (71.4)	122 (28.6)	197 (74.1)	69 (25.9)	107 (66.9)	53 (33.1)
Age, yrs	60 (47-72)	64 (57-70)*	59 (47-70)	64 (57-70)*	64 (48-74)	67 (55-73)
Duration, months	6 (4-9)	6 (3-8)	6 (4-9)	6 (3-8)	6 (5-9)	6 (3-8)*
RF, n (%)	198 (65.1)	73 (59.8)	158 (80.2)	56 (81.2)	40 (37.4)	17 (32.1)
DAS28, mean (SD)	4.8 (1.43)	4.7 (1.58)	4.7 (1.46)	4.9 (1.48)	4.9 (1.37)	4.5 (1.70)
HAQ	0.88 (0.5-1.38)	0.88 (0.25-1.13)	0.88 (0.5-1.38)	0.81 (0.25-1.13)	1.0 (0.5-1.5)	0.88 (0.25-1.25)
CRP, mg/L	7.3 (0.6-22)	13 (1.5-35.5)*	7.3 (0.6-23)	14 (2.3-36)*	6.3 (0-17.2)	11 (0.3-35)
ESR, mm/h	23 (12-44)	25 (12-49)	25 (14-47)	30 (15-55)	20 (10-36)	20 (11-35)
SJC28	6 (3-9)	8 (4-12)*	5 (3-9)	7 (4-11)*	6 (4-11)	8 (5-12)
TJC28	5 (2-10)	4 (1-9)	5 (2-9)	5 (1-9)	8 (4-11)	4 (0-9)*
Methotrexate, n (%)	193 (63.5)	70 (57.4)	124 (62.9)	36 (52.2)	69 (64.5)	34 (64.2)
bDMARDs, n (%)	15 (4.9)	9 (7.4)	11 (5.6)	8 (11.6)	4 (3.7)	1 (1.9)

Data are in median (IQR) unless otherwise indicated. * $P < 0.05$ vs female patients. ACPA: anticitrullinated peptide antibody; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; SJC28: swollen joint count in 28 joints; TJC28: tender joint count in 28 joints.

Table 3. Clinical remission (DAS28 < 2.6) and EULAR good response, according to ACPA status and sex.

Cohort	Outcome	6 months						12 months					
		ACPA Positive			ACPA Negative			ACPA Positive			ACPA Negative		
		Females	Males	*P*	Females	Males	*P*	Females	Males	*P*	Females	Males	*P*
Cohort I													
	Patients, n	81	33	–	62	26	–	86	36	–	62	24	–
	Remission	13 (16)	6 (18)	0.78	10 (16)	10 (38)	**0.02**	16 (19)	7 (19)	0.91	11 (18)	12 (50)	**0.002**
	EULAR good response	14 (17)	6 (18)	0.91	15 (24)	7 (27)	0.79	14 (16)	7 (19)	0.67	12 (19)	11 (46)	**0.01**
Cohort II													
	Patients, n	48	15	–	16	10	–	54	18	–	19	13	–
	Remission	15 (31)	8 (53)	0.12	5 (31)	5 (50)	0.34	22 (41)	6 (33)	0.56	2 (10)	6 (46)	**0.02**
	EULAR good response	24 (50)	9 (60)	0.50	7 (44)	6 (60)	0.42	23 (43)	10 (56)	0.34	3 (16)	6 (46)	0.06
Pooled													
	Patients, n	129	48	–	78	36	–	140	54	–	81	37	–
	Remission	28 (22)	14 (29)	0.30	15 (19)	15 (42)	**0.01**	38 (27)	13 (24)	0.66	13 (16)	18 (49)	**< 0.001**
	EULAR good response	38 (29)	15 (31)	0.82	22 (28)	13 (36)	0.39	37 (26)	17 (31)	0.48	15 (18)	17 (46)	**0.002**

Data are in n (%) unless otherwise indicated. Values in bold are statistically significant. ACPA: anticitrullinated peptide antibody; DAS28: Disease Activity Score in 28 joints; EULAR: European Alliance of Associations for Rheumatology.

with the online version of this article). Further, results observed in the pooled cohort were in accordance with those observed in the analysis of cohorts I and II (Table 3).

Predictors of response. The multivariate logistic regression model showed that male sex predicted DAS28 disease remission at 6 and 12 months in the patients who were ACPA negative in the pooled cohort (6 months: OR 2.78, 95% CI 1.11-6.99; 12 months: OR 4.79, 95% CI 1.97-11.6; Table 4). However, sex had no predictive value in the ACPA-positive group. Similar results were observed when analyzing EULAR good response as the outcome, and in separate analyses of cohort I and cohort II (Table 4). A strong predictive value of male sex in the patients who were ACPA negative was also demonstrated when using the more stringent CDAI remission as the outcome (Supplementary Table S3, available with the online version of this article).

In a nonstratified regression model with DAS28 remission at 12 months as the outcome, there was a statistically significant interaction between sex and ACPA status (adjusted P = 0.004; Table 5). There was a similar interaction in the analysis with CDAI remission as the outcome (adjusted P = 0.04; Supplementary Table S4, available with the online version of this article).

There was improvement in all DAS28 subcomponents in each of the sex- and ACPA status–based subgroups, in particular during the first 6 months (Figure). The best outcome for all subcomponents was observed in male patients who were ACPA negative. In contrast to the other subgroups, the median ESR and the median swollen joint count increased between 6 and 12 months in female patients with ACPA-negative RA (Figures A,B).

DISCUSSION

In the present observational study, which included 426 patients with early RA, we found that disease remission was achieved in a minority of patients with RA. The proportion of patients in remission was particularly low among females with ACPA-negative RA. Moreover, we showed that male sex was a predictor of better clinical outcome in patients with ACPA-negative RA, whereas there was no such association in patients with ACPA-positive RA. The results were similar in the 2 cohorts, with greater precision in the pooled cohort because of better statistical power to detect a difference in outcome. Both original cohorts included patients with early RA, with similar demographic and clinical characteristics. In both cohorts, patients received early treatment with conventional synthetic

Table 4. Multivariate logistic regression for the predictive value of sex according to ACPA status.

	Cohort I, OR (95% CI)[a,b]		Cohort II, OR (95% CI)[a,b]		Pooled Cohort, OR (95% CI)[a,b]	
	ACPA Positive	ACPA Negative	ACPA Positive	ACPA Negative	ACPA Positive	ACPA Negative
6 months						
Remission	1.15 (0.47-4.69)	2.87 (0.92-8.98)	3.35 (0.92-12.2)	1.85 (0.34-10.0)	1.78 (0.80-3.96)	2.78 (1.11-6.99)
EULAR good response	1.03 (0.34-3.13)	1.28 (0.43-3.79)	1.52 (0.45-5.20)	1.74 (0.31-9.74)	1.07 (0.50-2.28)	1.54 (0.64-3.72)
12 months						
Remission	1.39 (0.48-4.03)	4.62 (1.61-13.2)	0.87 (0.25-3.01)	6.87 (1.01-46.5)	1.06 (0.49-2.30)	4.79 (1.97-11.6)
EULAR good response	1.39 (0.49-3.96)	4.16 (1.37-12.6)	2.06 (0.59-7.20)	5.65 (0.93-34.4)	1.40 (0.67-2.95)	4.14 (1.68-10.2)

[a] Adjusted for DAS28, HAQ, and age at baseline. [b] Female = reference. ACPA: anticitrullinated peptide antibody; DAS28: Disease Activity Score in 28 joints; EULAR: European Alliance of Associations for Rheumatology; HAQ: Health Assessment Questionnaire; OR: odds ratio.

Table 5. Multivariable logistic regression for the relationship between sex and ACPA status, and their interaction with outcomes in early RA in the pooled cohort.

Outcome	Covariate	Basic Model, OR (95% CI)	Adjusted Model, OR (95% CI)[a]
DAS28 remission at 6 months	Male sex	3.00 (1.26-7.16)	2.96 (1.21-7.26)
	ACPA positive	1.16 (0.58-2.35)	1.13 (0.55-2.31)
	Interaction: sex × ACPA	0.49 (0.16-1.56)	0.54 (0.17-1.76)
EULAR good response at 6 months	Male sex	1.44 (0.62-3.33)	1.53 (0.65-3.62)
	ACPA positive	1.06 (0.57-1.98)	1.04 (0.55-1.95)
	Interaction: sex × ACPA	0.76 (0.25-2.28)	0.66 (0.21-2.04)
DAS28 remission at 12 months	Male sex	4.95 (2.06-11.9)	5.36 (2.18-13.19)
	ACPA positive	1.95 (0.97-3.93)	1.90 (0.93-3.87)
	Interaction: sex × ACPA	0.17 (0.05-0.54)	0.18 (0.06-0.58)
EULAR good response at 12 months	Male sex	3.74 (1.59-8.80)	4.25 (1.75-10.27)
	ACPA positive	1.58 (0.80-3.10)	1.56 (0.79-3.10)
	Interaction: sex × ACPA	0.34 (0.11-1.02)	0.29 (0.09-0.92)

[a] Adjusted for the variables in the table and for DAS28, HAQ, and age at baseline. ACPA: anticitrullinated peptide antibody; DAS28: Disease Activity Score in 28 joints; EULAR: European Alliance of Associations for Rheumatology; HAQ: Health Assessment Questionnaire; OR: odds ratio; RA: rheumatoid arthritis.

DMARDs to a similar extent in females and males. Further, patients were followed in a standardized manner in the same healthcare setting. Based on these similarities, the patients were pooled into a single cohort. However, a higher proportion of patients in cohort II were treated with bDMARDs during follow-up because of the difference in time of inclusion between the 2 cohorts. Moreover, the concept of "treat to target"[4] was well established during the period of enrollment in cohort II, whereas it was not established at the end of the 1990s when enrollment of cohort I took place. Still, findings from both cohorts indicated that females with ACPA-negative early RA represent a difficult-to-treat group of patients with RA.

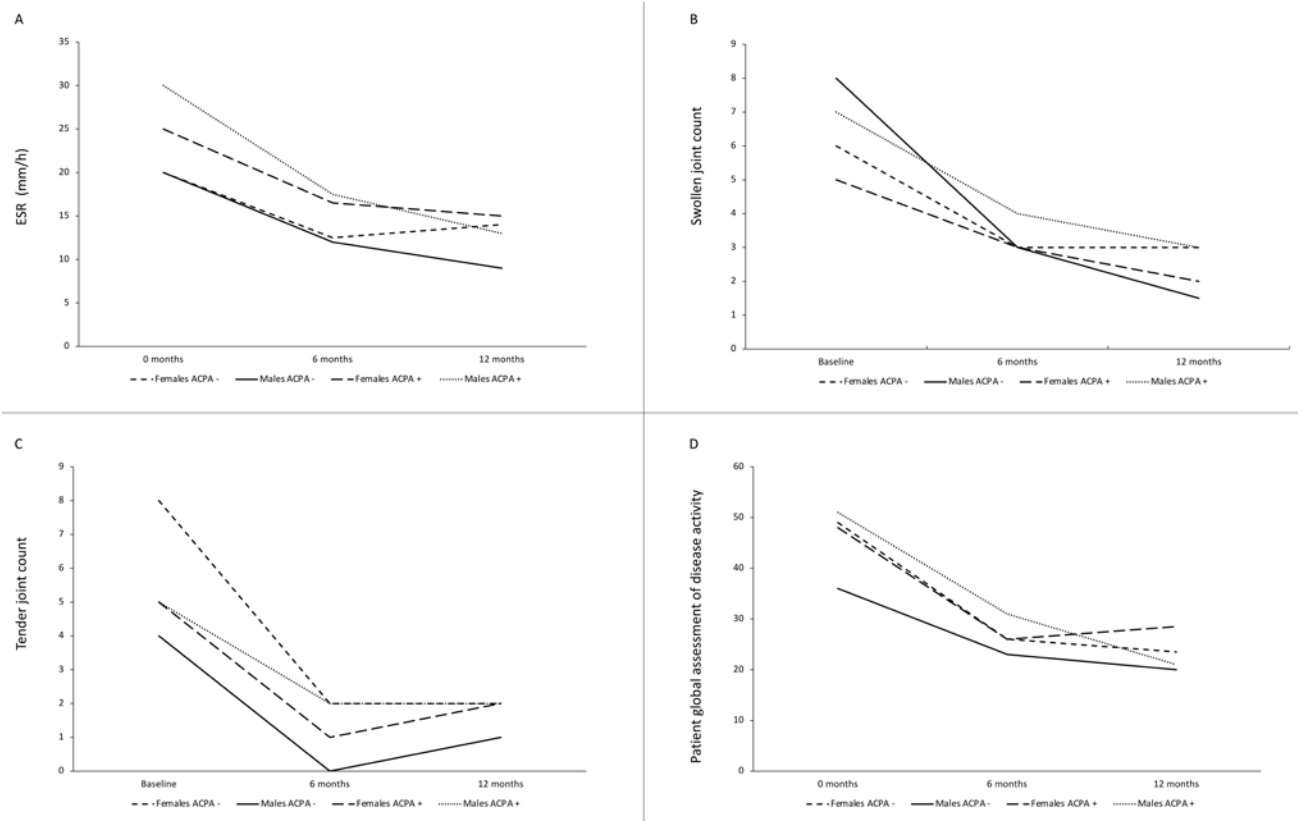

Figure. Changes in DAS28 subcomponents in sex- and ACPA status–based subgroups. (A) Change in ESR over time (median); (B) change in swollen joint count over time (median); (C) change in tender joint count over time (median); and (D) change in patient global assessment of disease activity over time (mean). ACPA: anticitrullinated peptide antibody; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate.

The predictive role of sex for clinical outcomes in RA has been extensively investigated, yielding conflicting results.[9,10,18,29,30,32-34] However, the present study was the first to explore the role of sex in RA according to ACPA status, to our knowledge. Indeed, to date, only 1 study has investigated predictors of treatment outcomes in seronegative early RA, but the results did not show any association between sex and outcome.[35] Of note, in contrast to the present study, that report investigated patients with RA who were seronegative for both RF and ACPA; moreover, the chosen primary outcome was EULAR good or moderate response vs nonresponse, and follow-up was not standardized. Our findings fill an important knowledge gap, as ACPA is a well-known marker of more aggressive disease,[13] and the prognostic value of sex is unclear. One possible explanation for our findings is that disease activity in females with ACPA-negative RA was partly driven by noninflammatory joint pain. Indeed, fibromyalgia, which is often associated with RA, and other widespread musculoskeletal pain syndromes are more prevalent in females,[36-38] and ACPA negativity has been reported to be a risk factor for fibromyalgia diagnosis in patients with RA.[39] It is well known that noninflammatory pain does not respond to immunosuppressive treatment. Further, ESR is known to be higher in females than in males,[40] thus accounting for sex differences in the DAS28. Therefore, the higher disease activity in female patients may not represent truly active inflammation, but rather a misclassification of disease activity. Indeed, a recent post hoc analysis of the GO-BEFORE (Golimumab Before Employing Methotrexate as the First-Line Option in the Treatment of Rheumatoid Arthritis of Early Onset) and GO-FORWARD (Golimumab for Subjects with Active Rheumatoid Arthritis despite Methotrexate Therapy) randomized controlled trials of golimumab[41,42] showed that women were less likely to achieve DAS28 remission than men, but there were no significant differences in the magnetic resonance imaging scores for synovitis.[43]

ACPA-negative RA may present a diagnostic challenge. The higher pain perception in females[44,45] and the limited reliability of manual joint count in the detection of swollen joints[46] may contribute to the misclassification of women who are ACPA negative as having RA. Although all patients fulfilled the established classification criteria for RA, we cannot exclude misclassification in our cohorts. However, this study represents a community-based sample of patients diagnosed with RA by a rheumatologist and should be applicable to clinical practice. Sex differences in patient-reported outcomes may also reflect secondary pain syndromes in patients with RA, or particular difficulties in assigning appropriate treatment to women with ACPA-negative RA.

An alternative explanation for the association between female sex and worse treatment outcome in ACPA-negative RA could be grounded in the influence that sex hormones have on the pathophysiology of synovitis in RA.[17] However, in this case, we would expect more consistent results across outcomes and studies in the literature.[9,10,18,29,30,32-34] Further, this hypothesis cannot explain why, in our cohort, sex was a clear negative prognostic factor in seronegative patients only.

Limitations of the present study are mainly due to missing data, in particular in cohort II, leading to limited precision in the logistic regression models. However, point estimates were similar in both cohorts, and they were robust in the pooled cohort. The observational design may not be the best option to assess treatment response in a population of patients because of treatment channeling of patient groups to certain therapies. However, we did not find significant differences in the type of treatment between women and men or between patients who were ACPA positive and those who were ACPA negative. Further, the observational design of the study better reflects the real-life setting, thus giving valuable information to rheumatologists involved in daily clinical practice. The homogeneity of our patient population and the standardized follow-up of the patients represent additional strengths of our study.

In conclusion, the present study investigated the influence of sex on clinical outcomes of early ACPA-negative and ACPA-positive RA. In 2 observational cohorts, male sex was a predictor of favorable outcomes in patients who were ACPA negative, whereas there were no such associations in patients who were ACPA positive. This suggests that females with ACPA-negative early RA represent a difficult-to-treat patient population. Since the present study is the first to investigate the relationship between sex and outcome in both ACPA-positive and ACPA-negative early RA, our findings should be replicated in other studies in order to determine generalizability.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum 2010;62:1576-82.
2. Yelin E, Trupin L, Wong B, Rush S. The impact of functional status and change in functional status on mortality over 18 years among persons with rheumatoid arthritis. J Rheumatol 2002;29:1851-7.
3. Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. Arthritis Rheum 2003; 48:1530-42.
4. Smolen JS, Aletaha D, Bijlsma JWJ, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
5. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685-99.
6. Lv Q, Yin Y, Li X, et al. The status of rheumatoid factor and anti-cyclic citrullinated peptide antibody are not associated with the effect of anti-TNFα agent treatment in patients with rheumatoid arthritis: a meta-analysis. PLoS One 2014;9:e89442.
7. Isaacs JD, Cohen SB, Emery P, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. Ann Rheum Dis 2013;72:329-36.
8. Alemao E, Postema R, Elbez Y, Mamane C, Finckh A. Presence of anti-cyclic citrullinated peptide antibodies is associated with better treatment response to abatacept but not to TNF inhibitors

in patients with rheumatoid arthritis: a meta-analysis. Clin Exp Rheumatol 2020;38:455-66.
9. Jawaheer D, Olsen J, Hetland ML. Sex differences in response to anti-tumor necrosis factor therapy in early and established rheumatoid arthritis -- results from the DANBIO registry. J Rheumatol 2012;39:46-53.
10. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol 2007;34:1670-3.
11. Saevarsdottir S, Wallin H, Seddighzadeh M, et al. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis 2011;70:469-75.
12. Hider SL, Silman AJ, Thomson W, Lunt M, Bunn D, Symmons DPM. Can clinical factors at presentation be used to predict outcome of treatment with methotrexate in patients with early inflammatory polyarthritis? Ann Rheum Dis 2009;68:57-62.
13. Kastbom A, Strandberg G, Lindroos A, Skogh T. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). Ann Rheum Dis 2004;63:1085-9.
14. Ajeganova S, Huizinga TWJ. Rheumatoid arthritis: seronegative and seropositive RA: alike but different? Nat Rev Rheumatol 2015; 11:8-9.
15. Rydell E, Forslind K, Nilsson JÅ, Jacobsson LTH, Turesson C. Smoking, body mass index, disease activity, and the risk of rapid radiographic progression in patients with early rheumatoid arthritis. Arthritis Res Ther 2018;20:82.
16. Eberhard A, Bergman S, Mandl T, et al. Predictors of unacceptable pain with and without low inflammation over 5 years in early rheumatoid arthritis—an inception cohort study. Arthritis Res Ther 2021;23:169.
17. Islander U, Jochems C, Lagerquist MK, Forsblad-d'Elia H, Carlsten H. Estrogens in rheumatoid arthritis; the immune system and bone. Mol Cell Endocrinol 2011;335:14-29.
18. Forslind K, Hafström I, Ahlmén M, Svensson B, BARFOT Study Group. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis 2007;66:46-52.
19. Listing J, Strangfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low--results from RABBIT, the German biologics register. Arthritis Res Ther 2006;8:R66.
20. Rydholm M, Book C, Wikström I, Jacobsson L, Turesson C. Course of grip force impairment in patients with early rheumatoid arthritis over the first five years after diagnosis. Arthritis Care Res 2018;70:491-8.
21. 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.
22. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
23. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
24. Ekdahl C, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis. Use of a Swedish version of the Stanford Health Assessment Questionnaire. Scand J Rheumatol 1988;17:263-71.
25. Eriksson JK, Askling J, Arkema EV. The Swedish Rheumatology Quality Register: optimisation of rheumatic disease assessments using register-enriched data. Clin Exp Rheumatol 2014;32:S-147-9.
26. Fransen J, van Riel PLCM. DAS remission cut points. Clin Exp Rheumatol 2006;24:S-29-32.
27. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/ International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34-40.
28. Burmester GR, Ferraccioli G, Flipo RM, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum 2008;59:32-41.
29. Kristensen LE, Kapetanovic MC, Gülfe A, Söderlin M, Saxne T, Geborek P. Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology 2008;47:495-9.
30. Hyrich KL, Watson KD, Silman AJ, Symmons DPM. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology 2006;45:1558-65.
31. Krams T, Ruyssen-Witrand A, Nigon D, et al. Effect of age at rheumatoid arthritis onset on clinical, radiographic, and functional outcomes: the ESPOIR cohort. Joint Bone Spine 2016;83:511-5.
32. Leffers HC, Ostergaard M, Glintborg B, et al. Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis 2011;70:1216-22.
33. Soliman MM, Hyrich KL, Lunt M, Watson KD, Symmons DPM, Ashcroft DM. Effectiveness of rituximab in patients with rheumatoid arthritis: observational study from the British Society for Rheumatology Biologics Register. J Rheumatol 2012;39:240-6.
34. Cagnotto G, Willim M, Nilsson JÅ, et al. Abatacept in rheumatoid arthritis: survival on drug, clinical outcomes, and their predictors-data from a large national quality register. Arthritis Res Ther 2020;22:15.
35. Lukas C, Mary J, Debandt M, et al. Predictors of good response to conventional synthetic DMARDs in early seronegative rheumatoid arthritis: data from the ESPOIR cohort. Arthritis Res Ther 2019;21:243.
36. Ben-Ami Shor D, Weitzman D, Dahan S, et al. Adherence and persistence with drug therapy among fibromyalgia patients: data from a large health maintenance organization. J Rheumatol 2017;44:1499-506.
37. Croft P, Rigby AS, Boswell R, Schollum J, Silman A. The prevalence of chronic widespread pain in the general population. J Rheumatol 1993;20:710-3.
38. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19-28.
39. Lee YC, Lu B, Boire G, et al. Incidence and predictors of secondary fibromyalgia in an early arthritis cohort. Ann Rheum Dis 2013;72:949-54.
40. Miller A, Green M, Robinson D. Simple rule for calculating normal erythrocyte sedimentation rate. Br Med J 1983;286:266.
41. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind,

placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009;60:2272-83.
42. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009;68:789-96.
43. Maynard C, Mikuls TR, Cannon GW, et al. Sex differences in the achievement of remission and low disease activity in rheumatoid arthritis. Arthritis Care Res 2020;72:326-33.
44. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth 2013;111:52-8.
45. Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. J Gen Intern Med 2001;16:266-75.
46. Cheung PP, Gossec L, Mak A, March L. Reliability of joint count assessment in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum 2014;43:721-9.