Sex and RA outcome

MALE SEX PREDICTS A FAVORABLE OUTCOME IN EARLY ACPA-NEGATIVE RHEUMATOID ARTHRITIS: DATA FROM AN OBSERVATIONAL STUDY.

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Key Indexing Terms

Rheumatoid arthritis

Outcomes

Sex

ABSTRACT

Objective. The aim of the present study was to investigate if the relation between sex and clinical outcomes in early rheumatoid arthritis varies by autoantibody status.

Methods. Two inception cohorts of consecutive patients with early RA (symptom duration ≤12 months) in the Southern Region of Sweden were investigated. Patients were stratified by anti-citrullinated peptide antibody (ACPA) status. The primary outcome was remission (DAS28<2.6) at 12 months. Secondary outcomes were remission at 6 months and EULAR good response compared to baseline at 6 and 12 months. In logistic regression models, adjusted for age, DAS28 and HAQ at baseline, the relation between sex and clinical outcomes, stratified by ACPA status, was investigated.

Results. In total 426 patients with early RA were included, 160 ACPA-negative and 266 ACPA-positive. At 12 months, 27% of females and 24% of males with ACPA-positive RA achieved DAS28 remission. In ACPA-negative RA, 16% of females and 49% 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 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.

1.BACKGROUND

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a prevalence of about 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 RA patients has improved in the last years, due to earlier and more intensive treatment strategies and to the development of several effective drugs with a favorable safety profile [4]. However, a substantial proportion of patients still has an unsatisfactory treatment response and needs to try multiple drugs to achieve the desired outcome [5]. Investigators have tried to find predictors of treatment outcome 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]. Anti-citrullinated peptide antibodies (ACPA), usually analyzed as anti-cyclic citrullinated peptide (anti-CCP) antibodies, are used both as 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 RA patients included in randomized clinical trials is 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 recently 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 [18-20]. To our knowledge, no previous studies have investigated the relation 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 ACPA-positive and ACPA-negative early RA patients.

2.PATIENTS AND 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 (symptom duration ≤12 months), recruited in 1995-2005 [15,21]. The patients were diagnosed with RA by a rheumatologist and fulfilled the 1987 revised American College of Rheumatology (ACR) classification criteria for RA [22]. The ACR/European League Against Rheumatism (ACR/EULAR) 2010 classification criteria for RA [23] were fulfilled by at least 88% of the patients [16]. The cohort included individuals from a defined area, the city of Malmö, Sweden (population 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 four rheumatologists in private practice in Malmö. Patients were followed according to a structured program as previously described [16]. Disease activity was measured by disease activity score in 28 joints (DAS28) [24], and disability was evaluated using the Swedish validated version of the health assessment questionnaire (HAQ) [25]. 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, US). 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 was reported by the laboratory as <9 mg/l.

Cohort II consisted of patients with early (≤ 12 months of symptom duration) RA according to the 1987 revised ACR criteria [22] or the 2010 ACR/EULAR classification criteria for RA [23], that had been diagnosed and followed at the outpatient rheumatology clinic of Skåne University Hospital in 2012-2016 and included in the Swedish Rheumatology Quality (SRQ) register [26]. SRQ is a nationwide Swedish clinical register of patients with chronic inflammatory joint diseases, including RA [26]. The SRQ covers clinical information on disease characteristics, including DAS28 and HAQ, and anti-rheumatic 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 was retrieved from the clinical records. During the study period, ACPA were assessed using standard ELISA methods for anti-CCP2 at the immunology laboratories of Skåne University Hospital, and IgM RF was analyzed using ELISA, as described above. ESR and high sensitivity CRP were assessed according to standard methods at the Department of Clinical Chemistry, Skåne University Hospital. Clinical disease activity index (CDAI) was estimated post-hoc in patients of both the 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 analogue 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): value of 0 in the Likert scale were reported as 0.5

cm in the new VAS, values of 1 corresponded to 2.0 cm, 2 to 4.0 cm, 3 to 7.0 cm, 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-up were represented by data from visits closest to 6 and 12 months from inclusion within time windows of 5-8 months and 10-15 months, respectively. Missing data from 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 ACPA-negative and ACPA-positive RA patients achieving clinical remission (DAS28 <2.6) [27] at 12 months. Secondary outcomes were the proportions achieving DAS28 remission at 6 months, or a EULAR good response [28] compared to baseline at 6 and 12 months. 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 data on DAS28 at baseline were included in the analyses. Baseline features in females and males, stratified by ACPA status, were compared using the Chi-square test, Mann-Whitney U test or 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 variable and sex as covariate. The odds ratio (OR) for each outcome was estimated and a 95% confidence interval (CI) was calculated. Analyses were stratified by ACPA status and presented separately for ACPA-positive and ACPA-negative patients. We also added a non-stratified model with an interaction term (sex*ACPA status) to determine whether ACPA status acted as an effect modifier on the association between sex and clinical outcomes. As baseline DAS28 influences the chance of achieving remission or a EULAR good response, all analyses were adjusted for DAS28 at baseline. As high HAQ is an established negative predictor of treatment response [29-31], all models were also adjusted for baseline HAQ. Furthermore, adjustment for age was also performed, since younger patients seem to have a better clinical outcome in early RA [32].

Analyses were performed for each cohort and after pooling Cohort I and Cohort II data. Statistical analysis was performed using IBM SPSS Statistics version 27.

3.RESULTS

Baseline characteristics in Cohort I

A total of 233 patients were evaluated. Two-hundred and twenty-five patients had data on DAS28 at baseline. Of these, 130 patients (92 females, 38 males) were ACPA-positive and 95 (66 females, 29 males) were ACPA-negative. Demographic and clinical disease characteristics at baseline were comparable between ACPA-negative and ACPA-positive patients, 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. Two-hundred and one patients had available data on DAS28 at baseline, 136 ACPA-positive (105 females, 31 males) and 65 ACPA-negative (41 females, 24 males) (Table 1). Disease characteristics at baseline were similar between ACPA-positive and ACPA-negative patients 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 bDMARDs between ACPA-positive female and male patients ($p<0.05$). However, treatment regimens were similar in male and female patients at 12 months (Supplementary material, Table S1).

TABLE 1

Baseline characteristics in Pooled Cohort

Four-hundred and twenty-six 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 also between females and males in the two 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 and Supplementary material, Table S1).

TABLE 2

Outcomes

In the Pooled Cohort, 26% of the ACPA-positive and 26% of the ACPA-negative patients achieved DAS28 remission at 12 months. A higher proportion of male patients were in remission at 6 and 12 months as compared to females in the ACPA-negative subset (Table 3). Males also had a higher likelihood of a major treatment response than females at 12 months. Sex-related differences in outcomes were not observed in the ACPA-positive patient subset. (Table 3). Similar results were observed when using CDAI remission as outcome (Supplementary material, Table S2). Furthermore, results observed in the Pooled Cohort were in accordance with those observed in analysis of Cohort I and II (Table 3).

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 ACPA-negative patients in the Pooled Cohort (OR 2.78; 95% CI 1.11-6.99 at 6 months; OR 4.79; 95% CI 1.97-11.6 at 12 months) (Table 4). However, sex had no predictive value in the ACPA-positive group. Similar results were observed when analyzing EULAR good response as an outcome, and in separate analyses of Cohort I and Cohort II (Table 4). A strong predictive value of male sex in the ACPA-negative patients was also demonstrated when using the more stringent CDAI remission as outcome (Supplementary material, Table S3).

In a non-stratified 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 analysis with CDAI remission as the outcome (adjusted p=0.04) (Supplementary material, Table S4).

TABLE 4

TABLE 5

There was improvement in all DAS28 subcomponents in each of the sex and ACPA-status based subgroups, in particular during the first 6 months (Fig 1). The best outcome for all subcomponents was observed in ACPA negative male patients. 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 (Fig 1 A, B).

FIGURE 1

4.DISCUSSION

In the present observational study, which included 426 patients with early RA, we found that disease remission was achieved in a minority of RA patients. 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 ACPA positive RA. The results were similar in the two cohorts, with greater precision in the Pooled Cohort due to 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 DMARDs (csDMARDs) to a similar extent in females and males. Furthermore, patients were followed in a standardized manner in the same health-care 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 due to difference in time of inclusion between the two 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 RA patients.

The predictive role of sex for clinical outcomes in RA has been extensively investigated, yielding conflicting results [9,18,19,30,31,33-35]. However, the present study was the first to explore the role of sex in RA according to ACPA status. Indeed, to date only one study has investigated predictors of treatment outcomes in seronegative early RA, but the results did not show any association between sex and outcome [36]. Of note, in contrast to the present study, this report investigated RA patients that were seronegative for both RF and ACPA; moreover, the chosen primary outcome was EULAR good or moderate response versus non-response 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 non-inflammatory joint pain. Indeed, fibromyalgia, which is often associated with RA, as well as other widespread musculoskeletal pain syndromes are more prevalent in females [37-39] and ACPA negativity has been reported to be a risk factor for fibromyalgia diagnosis in patients with RA [40]. It is well-known that non-inflammatory pain does not respond to immunosuppressive treatment. Furthermore, ESR is known to be higher in females than in men [41], thus accounting for sex differences in DAS28. Therefore, the higher disease activity in female patients may not represent a truly active inflammation, but rather a misclassification of disease activity. Indeed, a recent post-hoc analysis of the GO-BEFORE and GO-FORWARD RCTs of golimumab [42,43] showed that women were less likely to achieve DAS28 remission than men, but there were no significant differences in the magnetic resonance imaging score for synovitis [44].

ACPA negative RA may present a diagnostic challenge. The higher pain perception in females [45,46] and the limited reliability of manual joint count in detection of swollen joints [47] may contribute to misclassification of ACPA-negative women as RA. Although all patients fulfilled established classification criteria for RA, we cannot exclude misclassification in our cohorts. On the other hand, 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 [9,18,19,30,31,33-35]. Furthermore, 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 robust in the Pooled Cohort. The observational design may not be the best option to assess treatment response in a population of patients, due to 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 ACPA-positive and ACPA-negative patients. Furthermore, the observational design of the study better reflects the real-life setting, thus giving valuable information to rheumatologists involved in the daily clinical practice. The homogeneity of our patient population as well as the standardized follow-up of the patients represent an additional strength of our study.

5.CONCLUSION

The present study investigated the influence of sex on clinical outcomes of early ACPA-negative and ACPA-positive RA. In two observational cohorts, male sex was a predictor of favorable outcomes in ACPA-negative patients, whereas there were no such associations in ACPA-positive patients. 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 relation between sex and outcome in both ACPA-positive and ACPA-negative early RA, our findings should be replicated in other studies in order to be generalized.

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Legend: Figure 1

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); D. Change in patient global assessment of disease activity over time (mean).

Table 1. Baseline characteristics of Cohort I and Cohort II

	Cohort I				Cohort II			
	ACPA +		ACPA -		ACPA +		ACPA -	
	Females	Males	Females	Males	Females	Males	Females	Males
Patients	92	38	66	29	105	31	41	24
Age, years	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)	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)
SJC 28	7 (4-9)	7 (5-12)	6 (4-11)	8 (7-12)*	4 (2-8)	6 (3-10)	6 (3-11)	9 (2-13)
TJC 28	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	11 (10.5)	8 (25.8)*	4 (9.8)	1 (4.2)

Values are median and interquartile range if not otherwise specified. RF= Rheumatoid factor. HAQ= Health assessment questionnaire. SJC 28= swollen joint count on 28 joint index. TJC 28= tender joint count on 28 joint index. bDMARDs= biologic DMARDs.

* $p<0.05$ vs female patients

Table 2. Baseline characteristics of the pooled cohort.

Pooled Cohort	Total		ACPA +		ACPA -	
	F	M	F	M	F	M
Patients n (%)	304 (71.4)	122 (28.6)	197 (74.1)	69 (25.9)	107 (66.9)	53 (33.1)
Age	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)
SR	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)*
MTX	193 (63.5)	70 (57.4)	124 (62.9)	36 (52.2)	69 (64.5)	34 (64.2)
bDMARDs	15 (4.9)	9 (7.4)	11 (5.6)	8 (11.6)	4 (3.7)	1 (1.9)

* $p<0.05$ vs female patients

Values are median and interquartile range if not otherwise reported.

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

Cohort	Outcome	6 months						12 months					
		ACPA +			ACPA -			ACPA +			ACPA -		
		F	M	p	F	M	p	F	M	p	F	M	p
Cohort I	Patients	81	33		62	26		86	36		62	24	
	Remission	13 (16)	6 (18)	0.78	10 (16)	10 (38)	**0.023**	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)	**0.013**
Cohort II	Patients	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)	**0.022**
	EULAR good response	24 (50)	9 (60)	0.5	7 (44)	6 (60)	0.42	23 (43)	10 (56)	0.34	3 (16)	6 (46)	0.061
Pooled	Patients	129	48		78	36		140	54		81	37	
	Remission	28 (22)	14 (29)	0.3	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**

Outcome data are reported as frequencies (%)

F=females, M=males

Table 4. Predictive value of sex according to ACPA status. Multivariate logistic regression. OR (95% CI). Female=reference.

	Cohort I		Cohort II		Pooled Cohort	
6 months	ACPA +	ACPA -	ACPA +	ACPA -	ACPA +	ACPA -
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	ACPA +	ACPA -	ACPA +	ACPA -	ACPA +	ACPA -
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)

Adjusted for DAS28, HAQ and age at baseline.

Table 5. Relation for sex, ACPA status and their interaction with outcomes in early RA in the pooled cohort. Multivariable logistic regression. OR (95 % CI)

Outcome	Covariate	Basic model	Adjusted model¶
6 months Remission	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	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)
12 months Remission	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	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)

¶Adjusted for the variables in the table and for DAS28, HAQ and age at baseline.

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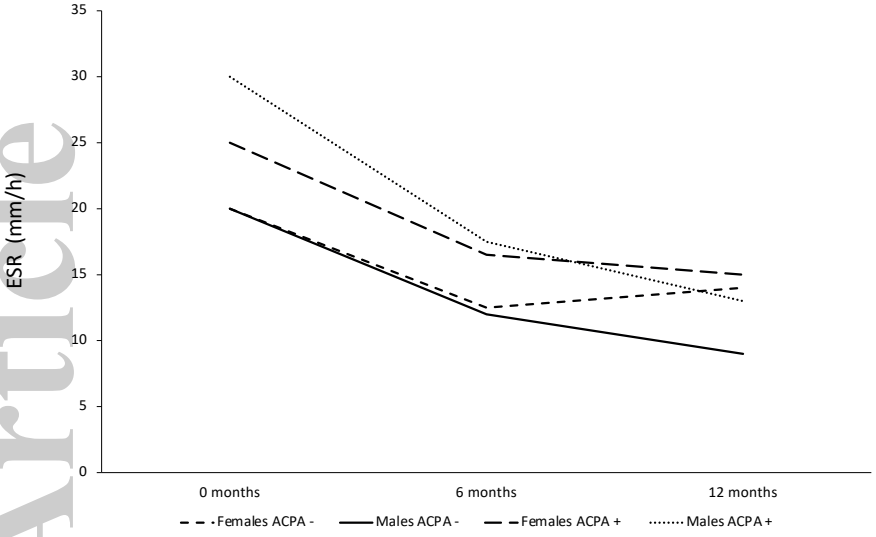

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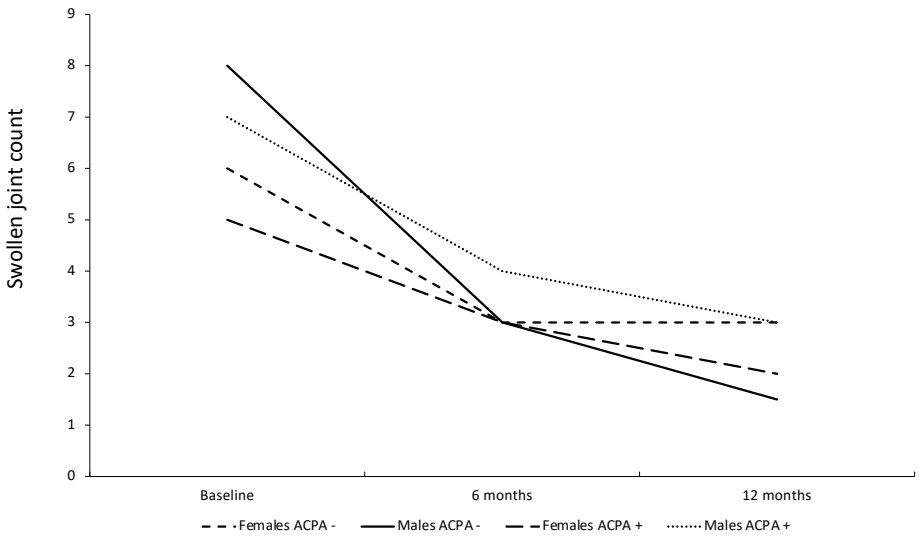

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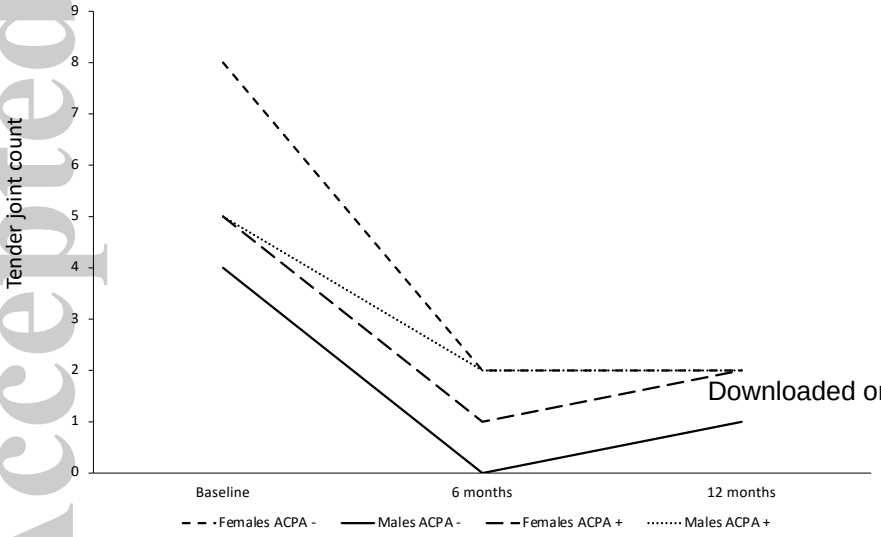

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