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# Although female patients with ankylosing spondylitis score worse on disease activity than male patients and improvement in disease activity is comparable, male patients show more radiographic progression during treatment with TNF-$\alpha$ inhibitors

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ABSTRACT

*Background:* The clinical presentation of ankylosing spondylitis (AS) differs between genders. Our aim was to investigate differences in disease activity, disease outcome and treatment response between male and female AS patients before and after starting tumor necrosis factor (TNF)-$\alpha$ inhibitors in daily clinical practice.
*Methods:* Patients from the Groningen Leeuwarden AS (GLAS) cohort who started TNF-$\alpha$ inhibitors and who had visits at baseline and after 3 months and/or 2 years of follow-up were included.
*Results:* Of 254 included AS patients, 69% were male. At baseline, female patients scored significantly higher on BASDAI, ASDAS, and tender entheses than male patients. In contrast, CRP, swollen joints, and history of extra-articular manifestations were comparable between genders. Women experienced significantly worse physical function and QoL, whereas men showed significantly more kyphosis and spinal radiographic damage. After 3 months and 2 years of follow-up, all clinical assessments improved significantly, with comparable mean change scores for female and male patients; mean 2-year change in BASDAI -2.7 vs. -2.7, ASDAS -1.50 vs. -1.68, tender entheses -2.4 vs. -1.4, CRP -8 vs. -8, BASFI -2.2 vs. -2.1 and ASQoL -5 vs. -4, respectively. Radiographic progression was significantly higher in male patients. Female patients switched more frequently to another TNF-$\alpha$ inhibitor during 2 years of follow-up (32% vs. 14%).
*Conclusion:* Although female patients experienced higher disease activity, worse physical function and quality of life, and switched TNF-$\alpha$ inhibitors more often, clinical improvement during treatment with TNF-$\alpha$ inhibitors was comparable between genders. However, male patients showed more radiographic spinal damage after 2 years.



## Introduction

Ankylosing spondylitis (AS) is a chronic auto-inflammatory rheumatic disease, in which the sacroiliac (SI) joints and the spine are mainly affected. As a result, AS patients suffer from chronic low back pain, progressive stiffness and reduced spinal mobility. Enthesitis, peripheral arthritis and extra-articular manifestations can also occur. These symptoms contribute to significant disability and reduction of quality of life [1,2].

The prevalence of AS according to the modified New York criteria is three times higher in male than in female patients, although prevalence according to the ASAS criteria for non-radiographic axial spondyloarthritis seems to be comparable between genders [3,4]. There are also differences in the clinical presentation of AS. Two cross-sectional cohort studies showed that female patients experience higher disease activity and worse physical function and health-related quality of life [5,6]. However, male patients are more prone to develop spinal radiographic damage [7–9].

Recent research using pooled data from four randomized controlled trials (RCTs) in AS showed that female patients showed less clinical improvement after 12 weeks of treatment with TNF-$\alpha$ inhibitors compared to male patients (10). Furthermore, multiple AS cohort studies have identified male gender as independent baseline predictor of good clinical response and continuation of treatment with TNF-$\alpha$ inhibitors [11–14].

In daily clinical practice, evaluating disease activity and outcome in AS is mostly based on patient-reported assessments. However, in general, it is known that men and women approach their own health and health-related problems differently [15,16].

To evaluate clinical outcome, it is important to have knowledge of potential differences between female and male AS patients, since this

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may have consequences for the interpretation of treatment response and therapy choices. Little is known about differences in clinical assessments between male and female AS patients before and after starting treatment with TNF-$\alpha$ inhibitors in daily clinical practice.

Therefore, our aim was to investigate differences in disease activity, disease outcome and treatment response between male and female AS patients before the start of TNF-$\alpha$ inhibitors and after 3 months and 2 years of follow-up in daily clinical practice.

## Materials and methods

### *Patients*

Data from consecutive outpatients fulfilling the modified New York criteria for AS, included in the Groningen Leeuwarden Ankylosing Spondylitis (GLAS) cohort between November 2004 and December 2012 were used for these analyses. The GLAS cohort is an ongoing prospective longitudinal observational cohort study, with a fixed protocol of follow-up visits [11]. Included were all biological treatment naïve patients, who started TNF-$\alpha$ inhibitors and had visits at baseline and after 3 months and/or 2 years of follow-up. According to the ASAS consensus statement, the criteria to start TNF-$\alpha$ inhibitors included persisted active disease according to the Bath AS Disease Activity Index (BASDAI $\geq$ 4) and positive expert opinion, despite of treatment with 2 different NSAIDs for 4 weeks [17]. Patients started with infliximab, etanercept or adalimumab. The GLAS cohort was approved by the ethics committees of the Medical Center Leeuwarden and University Medical Center Groningen. To participate in this study, all patients provided written informed consent according to the Declaration of Helsinki.

### *Clinical assessments*

Patients were evaluated at baseline (before starting TNF-$\alpha$ inhibitors) and after 3 months and 2 years of follow-up.

### *Disease activity*

Disease activity was assessed using the BASDAI, AS Disease Activity Score (ASDAS), C-reactive protein (CRP), enthesitis (number of tender entheses, 0–28), peripheral arthritis (number of swollen joints, range 0–44), and history of extra-articular manifestations (uveitis, psoriasis and inflammatory bowel disease). BASDAI of $\geq$ 4.0 indicated high disease activity. ASDAS between 1.3 and 2.0 was considered as mild disease activity, ASDAS between 2.1 and 3.4 as high disease activity and ASDAS of $\geq$ 3.5 as very high disease activity [18]. CRP level $<$ 5.0 mg/l was considered as normal [19,20].

### *Disease outcome*

Physical function was assessed using the Bath AS Functional Index (BASFI) and quality of life using the AS Quality of Life (ASQoL) questionnaire. The occiput-to-wall distance (OWD) was used to measure spinal kyphosis. Radiographic damage of the spine was assessed by two independent readers blinded for patient characteristics using the modified Stroke AS Spinal Score (mSASSS, range 0–72) [21]. This method uses the lateral view of radiographs of the cervical and lumbar spine to score spinal osteoproliferation on individual corners of the vertebrae.

### *Treatment response*

Criteria of continuation with TNF-$\alpha$ inhibitors were met in case of an improvement of $\geq$ 2 units in BASDAI (on a 0–10 scale) or improvement of $\geq$ 50% (BASDAI50 response) from baseline [22]. Clinical response to treatment was analyzed using the clinical important (CII) and major improvement (MI) in ASDAS, defined as $\geq$ 1.1 and $\geq$ 2.0 units of improvement from baseline, respectively [18]. The ASAS20 response was defined as $\geq$ 20% improvement in two years and absolute improvement of $\geq$ 1 unit in at least 3 of the 4 following domains: physical function (BASFI), spinal pain, patient's GDA, and morning stiffness (the mean from BASDAI's questions 5 and 6), with no worsening by more $>$ 20% in the remaining domain. ASAS40 response was defined as $\geq$ 40% improvement in two years and an absolute improvement of $\geq$ 2 units in at least 3 of the domains, with no worsening at all in the remaining domain. [23] Reasons for stopping TNF-$\alpha$ inhibitors or switching to another TNF-$\alpha$ inhibitor were divided into three categories: inefficacy, side effects o(23)r other (incl. pregnancy whish).

### *Statistical analysis*

Statistical analysis was performed using IBM SPSS Statistics 22 software (SPSS, Chicago, IL, USA). Differences between male and female AS patients in disease activity, disease outcome and clinical response to treatment were compared using Chi-square test (categorical data), independent samples T-test (normally distributed data) and Mann Whitney U test (non-normally distributed data). Differences were explored at baseline, 3 months and 2 years as well as change over time using the delta of 0–3 months and 0–2 years. Differences between male and female patients regarding the use of TNF-$\alpha$ inhibitors over 2 years, expressed as the percentage of patients stopping, switching and continuing TNF-$\alpha$ inhibitors, were compared using Chi-square test. P-values $\leq$ 0.05 were considered statistically significant.

## Results

In total, 265 biological naïve AS patients started with TNF-$\alpha$ inhibitors. Eleven patients were excluded; 7 patients had missing visits at baseline or at both follow-up visits and 4 patients were lost to follow-up (3 patients stopped follow-up within the GLAS cohort and one patient died) (Supplementary Fig. 1). Of the 254 included patients, 69% were male, and 82% were HLA-B27 positive. As expected, all patients had active disease at baseline (Table 1).

### *Gender differences at baseline*

Patient characteristics including age, disease duration, HLA B27 status, and BMI at baseline were comparable between genders. Before the start of TNF-$\alpha$ inhibitors, female patients scored significantly higher on patient-reported measures of disease activity than male patients, i.e. BASDAI, ASDAS, and tender entheses. Distinct objective assessments of disease activity were comparable between genders, i.e. CRP, peripheral arthritis (swollen joints), and history of extra-articular manifestations (uveitis, psoriasis, IBD). At baseline, female patients also scored significantly worse on patient-reported measures of disease outcome, i.e. physical function (BASFI) and quality of life (ASQoL). In contrast, male patients showed significantly more spinal kyphosis (OWD) and spinal radiographic damage (mSASSS) (Table 1). See Supplementary Fig. 2 for a graphical view of the distribution of scores in male and female patients.

### *Change in clinical assessments after 3 months and 2 years*

The overall group showed significant improvement in clinical assessments of disease activity, physical function, quality of life, and spinal mobility after starting TNF-$\alpha$ inhibitors. Changes in these clinical assessments over 3 months and 2 years were comparable between male and female patients (Table 2). Furthermore, the proportion of patients showing BASDAI and ASDAS response after 3 months and 2 years was also comparable between genders

**Table 1**
Patient characteristics and clinical assessments of all, female and male AS patients at baseline

| | All patients ($n$ = 254) | Female ($n$ = 78) | Male ($n$ = 176) | $P$-value |
|---|---|---|---|---|
| *Patient characteristics* | | | | |
| Age (yrs) | 42.9 ± 12.0 | 41.1 ± 12.3 | 43.7 ± 11.9 | 0.116 |
| Time since diagnosis (yrs) | 7 (1–17) | 5 (1–14) | 8 (1–17) | 0.122 |
| Symptom duration (yrs) | 16 (8–25) | 13 (7–22) | 17 (9–26) | 0.158 |
| HLA-B27 + (n, %) | 202 (82) | 58 (76) | 144 (84) | 0.214 |
| BMI (kg/m$^2$) | 26.8 ± 4.5 | 27.7 ± 5.7 | 26.4 ± 3.8 | 0.117 |
| Current NSAID use (n, %) | 194 (84) | 58 (84) | 136 (85) | 1.000 |
| First TNF-$\alpha$ inhibitor (n, %) | | | | |
| Infliximab | 35 (14) | 15 (19) | 20 (11) | 0.215 |
| Etanercept | 155 (61) | 43 (55) | 112 (64) | |
| Adalimumab | 64 (25) | 20 (26) | 44 (25) | |
| History of uveitis (n, %) | 70 (28) | 20 (26) | 50 (29) | 0.652 |
| History of psoriasis (n, %) | 15 (6) | 4 (5) | 11 (6) | 1.000 |
| History of IBD (n, %) | 25 (10) | 7 (9) | 18 (10) | 0.823 |
| *Disease activity* | | | | |
| BASDAI (0–10) | 6.1 ± 1.7 | 6.5 ± 1.6 | 5.9 ± 1.7 | 0.004 |
| $ASDAS_{CRP}$ | 3.74 ± 0.86 | 3.93 ± 0.70 | 3.66 ± 0.92 | 0.024 |
| CRP (mg/l) | 13 (5–22) | 14 (6–25) | 12 (4–21) | 0.313 |
| CRP ≥ 5 mg/ (n, %) | 193 (77) | 64 (82) | 129 (74) | 0.199 |
| Tender entheses (0–28) | 3 (0–6) | 5 (2–8) | 2 (0–5) | 0.000 |
| ≥ 1 tender entheses (n, %) | 181 (71) | 63 (81) | 118 (67) | 0.035 |
| Swollen joints (0–44) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0.721 |
| ≥ 1 swollen joint (n, %) | 42 (17) | 14 (18) | 28 (16) | 0.717 |
| *Disease outcome* | | | | |
| BASFI (0 – 10) | 5.7 ± 2.1 | 6.2 ± 2.1 | 5.4 ± 2.1 | 0.013 |
| ASQoL (0 – 18) | 10 (7–13) | 12 (9–14) | 9 (7–12) | 0.000 |
| OWD (cm) | 4.0 (0.0–11.0) | 0.0 (0.0–7.8) | 5.0 (0.0–12.5) | 0.001 |
| mSASSS (0–72) | 5.5 (1.0–18.0) | 2.4 (0.9–7.6) | 7.8 (1.5–23.8) | 0.000 |

Values are presented as mean ± SD or median (interquartile range), unless otherwise indicated. *AS: ankylosing spondylitis; HLA-B27: Human leukocyte antigen B27; BMI: Body Mass Index; NSAID: non-steroidal anti-inflammatory drugs; BASDAI: Bath AS Disease Activity Index; ASDAS: AS Disease Activity Score; CRP: C-reactive protein; IBD: inflammatory bowel disease; BASFI: Bath AS Functional Index; ASQoL: AS Quality of Life; OWD: Occiput-to-Wall Distance; mSASSS: modified Stroke AS Spinal Score.*

**Table 2**
Change in clinical assessments and clinical response to treatment of all, female and male AS patients after 3 months and 2 years of follow-up

| | All patients ($n$ = 237) | Female ($n$ = 75) | Male ($n$ = 162) | $P$-value |
|---|---|---|---|---|
| *Change at 3 months* | | | | |
| BASDAI (0–10) | −2.7 ± 2.1 | −2.6 ± 2.2 | −2.8 ± 2.0 | 0.506 |
| BASDAI change ≥ 2.0 (n, %) | 155 (65) | 46 (61) | 109 (67) | 0.382 |
| BASDAI50 (n, %) | 119 (50) | 32 (43) | 87 (54) | 0.161 |
| $ASDAS_{CRP}$ | −1.66 ± 1.09 | −1.48 ± 1.06 | −1.74 ± 1.09 | 0.092 |
| ASDAS CII (n, %) | 158 (69) | 45 (62) | 113 (72) | 0.128 |
| ASDAS MI (n, %) | 84 (37) | 22 (30) | 62 (40) | 0.188 |
| ASAS20 (n, %) | 157 (68) | 44 (62) | 113 (71) | 0.220 |
| ASAS40 (n, %) | 116 (50) | 33 (46) | 83 (52) | 0.478 |
| CRP (mg/l) | −8 (−19 – −1) | −8 (−19– −1) | −9 (−19 – −1) | 0.592 |
| Tender entheses (0–28) | −1.6 ± 3.9 | −2.2 ± 4.7 | −1.3 ± 3.5 | 0.150 |
| Swollen joints (0–44) | −0.3 ± 0.9 | −0.3 ± 0.8 | −0.2 ± 1.0 | 0.613 |
| BASFI (0 – 10) | −1.9 ± 2.1 | −2.0 ± 2.2 | −1.9 ± 2.0 | 0.758 |
| ASQoL (0 – 18) | −5 (−8 – −2) | −6 (−10 – −1) | −4 (−7 – −2) | 0.354 |
| OWD (cm) | 0.0 (−2.0 – 0.0) | 0.0 (−1.5 – 0.0) | −0.5 (−2.2 – 0.0) | 0.148 |
| *Change at 2 years* | All patients (n = 221) | Female (n = 68) | Male (n = 153) | P-value |
| BASDAI (0–10) | −2.7 ± 2.0 | −2.7 ± 2.2 | −2.7 ± 2.0 | 0.923 |
| BASDAI change ≥ 2.0 (n, %) | 144 (65) | 42 (62) | 102 (67) | 0.541 |
| BASDAI50 (n, %) | 109 (49) | 31 (46) | 78 (51) | 0.470 |
| $ASDAS_{CRP}$ | −1.62 ± 1.09 | −1.50 ± 1.06 | −1.68 ± 1.10 | 0.258 |
| ASDAS CII (n, %) | 152 (71) | 44 (67) | 108 (74) | 0.328 |
| ASDAS MI (n, %) | 82 (39) | 26 (39) | 56 (38) | 0.880 |
| ASAS20 (n, %) | 149 (69) | 40 (63) | 109 (72) | 0.196 |
| ASAS40 (n, %) | 108 (50) | 31 (48) | 77 (51) | 0.882 |
| CRP (mg/l) | - 8 (−17–0) | −8 (−20 – 0) | −8 (−16 – 0) | 0.816 |
| Tender entheses (0–28) | −1.7 ± 4.1 | −2.4 ± 5.5 | −1.4 ± 3.3 | 0.200 |
| Swollen joints (0–44) | −0.5 ± 2.1 | −0.3 ± 0.9 | −0.5 ± 2.5 | 0.330 |
| BASFI (0 – 10) | −2.1 ± 2.2 | −2.2 ± 2.5 | −2.1 ± 2.1 | 0.657 |
| ASQoL (0 – 18) | −4 (−7 – −2) | −5 (−9 – −3) | −4 (−7 – −2) | 0.113 |
| OWD (cm) | 0.0 (−3.0 – 0.0) | 0.0 (−2.5 – 0.0) | 0.0 (−3.0 – 0.5) | 0.747 |
| mSASSS (0–72) | 1.0 (0.0–2.5) | 0.0 (0.0–1.2) | 1.0 (0.0–3.6) | 0.001 |

Values are presented as mean ± SD or median (interquartile range), unless otherwise indicated. *CII: clinically important improvement of ASDAS (change ≥ 1.1); MI: major improvement of ASDAS (change ≥ 2.0). See Table 1 for other abbreviations.*

(Table 2). The 2-year change in mSASSS was significantly higher in male patients than in female patients.

*Gender differences after 2 years*

After 2 years of follow-up, patient-reported measures of disease activity (BASDAI, ASDAS, tender entheses) remained significantly higher in female patients. This was also the case for quality of life (ASQoL). Physical function (BASFI) was comparable between female and male patients after 2 years and in contrast to baseline. Mean CRP was within the normal range but significantly higher in female patients than in male patients. Male patients still showed significantly more spinal kyphosis (OWD) and spinal radiographic damage (mSASSS) (Table 3). See supplementary Fig. 3 for a graphical view of the distribution in scores in male and female patients.

Subsequently, we compared the characteristics of patients with elevated and normal CRP levels after 2 years of follow-up. Female patients with elevated CRP levels were significantly older and had higher BMI compared to females with normal CRP levels. Male patients with elevated CRP levels had significantly longer disease duration and were more often HLA-B27 + compared to males with normal CRP levels (Supplementary Table 1).

*Female versus male: use of TNF-α inhibitors over time*

After 2 years of follow-up, 201 of the 254 patients (79%) were still using TNF-α inhibitors. Within the overall group, 84% ($n = 143$) of the male patients and 76% ($n = 58$) of the female patients ($p = 0.156$) were still using TNF-α inhibitors.

Significantly more male patients were using their first TNF-α inhibitor compared to female patients: 74% vs. 46% resp. ($p < 0.001$). The main reasons for stopping the first TNF-α inhibitor were inefficacy (59%) or side effects (27%), without significant differences between male and female patients.

In the overall group, 48 patients (19%) switched to a second TNF-α inhibitor during the 2 years of follow-up. Significantly more female patients switched to a second TNF-α inhibitor compared to male patients, 32% vs. 14% resp. ($p = 0.003$). Analyses of the 48 patients switching TNF-α inhibitors showed that significantly more male than female patients switched because of inefficacy (83% vs. 54%, $p = 0.047$) and more female than male patients switched because of side effects (42% vs. 13%; $p = 0.043$).

Of the patients still using TNF-α inhibitors after 2 years of follow-up ($n = 201$), all clinical assessments and the 2-year change in clinical assessments were comparable with the overall group ($n = 254$). (Supplementary Table 2).

## Discussion

This prospective observational longitudinal cohort study in daily clinical practice investigated the differences in clinical and outcome assessments between male and female AS patients before, at 3 months and at 2 years after the start of TNF-α inhibitors.

Before the start of TNF-α inhibitors female AS patients scored worse on patient-reported assessments BASDAI, BASFI, ASQoL and tender entheses than male patients. CRP, an objective measure of disease activity, did not differ significantly between genders before the start of the treatment. This indicates that the significantly higher ASDAS at baseline in women mainly results from the patient self-reported questions of the ASDAS. This suggests that, besides reporting ASDAS, it is of additional value to report CRP. These results confirm the results of our recent cross-sectional analysis of AS patients on either biological or conventional treatment, in which we showed that female patients experienced higher disease activity and worse physical function and quality of life [6]. In contrast, the outcome measure occiput to wall distance was significantly larger in male patients at baseline, reflecting increased spinal kyphosis. Conform other studies [4,7] worse outcome was also demonstrated by more spinal radiographic damage in male patients according to mSASSS.

In the present study, we found significant improvement of all clinical assessments over 3 months and 2 years, which indicates that treatment with TNF-α inhibitors was effective in both male and female AS patients. Interestingly, there were no significant differences in 3-month and 2-year changes in disease activity, including the ASAS 20 and 40 responses between male and female patients using TNF-α inhibitors.

In contrast, a recent study of pooled data from 4 RCTs showed that female patients tend to have less clinical improvement according to BASDAI, ASDAS and BASFI after 12 weeks of treatment with TNF-α inhibitors [10]. However, the difference in change of BASDAI and ASDAS between female and male patients between the pooled data study and our study was more or less comparable. The difference in change of BASDAI between male and female patients was 0.4 vs. 0.2, and the mean difference in change of ASDAS between genders was 0.21 vs. 0.26 (pooled data vs. our cohort). The pooled data study of van der Horst et al. analyzed a larger number of patients than our current study (1283 patients vs. 254 patients), which may explain why these relatively small differences in the pooled data study were statistically significant. Furthermore, at baseline, in de study of van der Horst et al., patient characteristics differed between genders in which they reported older age at disease onset, shorter symptom duration, a lower HLA-B27 positive rate and a lower CRP in female patients compared to male patients. These patient characteristics did not differ between genders in our cohort study. Additionally, recent Swiss and Italian cohort studies showed a lower rate of female patients

**Table 3**
Patient characteristics and clinical assessments of all, female and male AS patients after 2 years of follow-up

| | All patients ($n = 221$) | Female ($n = 68$) | Male ($n = 153$) | *P*-value |
|---|---|---|---|---|
| *Clinical assessments* | | | | |
| BMI (kg/m$^2$) | 26.9 ± 4.6 | 28.0 ± 5.6 | 26.5 ± 4.0 | 0.083 |
| BASDAI (0–10) | 2.8 (1.8–5.0) | 3.4 (2.2–5.6) | 2.6 (1.4–4.3) | 0.008 |
| $ASDAS_{CRP}$ | 2.13 ± 0.89 | 2.43 ± 0.92 | 2.00 ± 0.84 | 0.001 |
| CRP (mg/l) | 2 (2–7) | 4 (2–10) | 2 (2–5) | 0.003 |
| CRP ≥ 5 mg/l (n, %) | 75 (35) | 32 (47) | 43 (29) | 0.031 |
| Tender entheses (0–28) | 0 (0–3) | 2 (0–5) | 0 (0–2) | 0.000 |
| ≥ 1 tender entheses (n, %) | 106 (48) | 47 (69) | 59 (39) | 0.000 |
| Swollen joints (0–44) | 0 (0–0) | 0 (0–0) | 0 (0–0) | 0.538 |
| ≥ 1 swollen joint (n, %) | 13 (6) | 5 (7) | 8 (5) | 0.548 |
| BASFI (0 – 10) | 3.6 ± 2.4 | 4.0 ± 2.5 | 3.5 ± 2.4 | 0.110 |
| ASQoL (0 – 18) | 4 (1–8) | 6 (2–10) | 3 (0–8) | 0.028 |
| OWD (cm) | 2.3 (0.0–8.5) | 0.0 (0.0–3.0) | 4.0 (0.0–9.5) | 0.000 |
| mSASSS (0–72) | 7.3 (1.4–22.9) | 3.0 (0.5–8.0) | 11.4 (2.2–25.5) | 0.000 |

Values are presented as mean ± SD or median (interquartile range), unless otherwise indicated. *See Table 1 for other abbreviations.*

responding to TNF-α inhibitors, as well as a reduced treatment response compared to male patients. These studies showed higher CRP in male patients at baseline and in contrast to our study a comparable BASDAI in men and women. This suggests a higher objective disease activity in male patients at baseline before the start of TNF-α inhibitors. The Swiss cohort also shows other differences in patient characteristics such as significantly more HLA-B27 positive male patients and a significantly higher BMI in male patients. These differences may also be confounding factors in relation to the results. Only the Swiss study did adjusted analyses to correct for these differences in patient characteristics in relation to ASAS and ASDAS response, but did not report change scores. Furthermore, different endpoints were used in the Swiss and Italian cohorts (i.e. ASAS 20 and ASAS 40 response). The difference between genders in our cohort in ASAS20 and ASAS40 response after two years was comparable with the differences in the response in the Swiss cohort after one year: in both studies there is a 10% change between genders in ASAS20 response, with in both cohorts a slightly higher percentage of male patients compared to female patients, but not significant.

In our current study a higher percentage of male patients (74%) fulfilled the ASDAS CII after two years, compared to the female patients (67%). Although this difference was not statistically significant this may have been influenced by the total number of patients and the relatively smaller number of women (31%) included in the analyses compared to men. Though, this gender distribution is usual for an AS cohort and comparable to other studies.

An interesting and novel finding of the present study is that the proportion of clinical responders considering BASDAI and ASDAS over 2 years was comparable between genders. In a previous analysis of our cohort, we showed that male gender was predictive for the BASDAI50 response after 3 months of treatment with TNF-α inhibitors [11]. The current results did not confirm this gender difference. Analyzing the data of both studies in more detail revealed that this gender difference in treatment response was only found in the AS patients included before 2009. This reflects changes in patient characteristics of AS patients starting TNF-α inhibitors over the past decade.

In the previous analysis of the same cohort, it was also shown that male gender is a prognostic factor for continuation of treatment with TNF-α inhibitors [11]. In the current analysis, significantly less female patients were still using their first TNF-α inhibitor and additionally more female patients switched to another TNF-α inhibitor as well. Despite these findings, there were no significant gender differences in short-term (3 months) and long-term (2 years) improvement in clinical assessments.

After 2 years of follow-up, subjective measures of disease activity were still significantly higher in female patients, compared to male patients. Strikingly, CRP was also significantly higher in female patients. Although statistically significant, the difference in CRP at 2 years between female and male patients was small, 4 vs. 2 mg/l respectively. The clinical relevance of this CRP difference is unsure since a CRP level $< 5.0$ mg/l is considered as normal.

Interestingly, additional analysis revealed differences in patient characteristics in relation to CRP levels after treatment with TNF-α inhibitors. Females with elevated CRP at two years were significantly older and had higher BMI compared to females with normal CRP, while male patients with elevated CRP showed longer disease duration and were more often HLA-B27 + compared to males with normal CRP levels.

The most important outcome, progression in spinal radiographic damage over 2 years was significantly higher in male patients. Previous AS studies showed that the presence of radiographic damage at baseline and male gender are prognostic factors for worse radiographic outcome [24]. Furthermore, a recent study in the same cohort of AS patients showed that patients at risk of poor radiographic outcome, show the largest long-term radiographic progression during treatment with TNF-α inhibitors [25].

In line with our findings, population-based studies demonstrated that women report pain more frequently than men [26,27]. The underlying mechanism of these gender differences is unknown, but multiple biological and psychosocial factors may play a role. For instance, the distribution of the sex hormones and their receptors in the nervous systems is associated with nociceptive transmission, which is responsible for pain after body tissue damage. The male hormone testosterone appears to be protective in nature since it is more anti-nociceptive [28]. On psychosocial level, it has been found that man and women have different pain coping strategies [29,30]. Furthermore, early exposure to environmental stress is associated with decreased pain sensitivity, which is mainly observed in women [31].

Further research is needed to evaluate if gender-specific thresholds for disease activity in AS are helpful in research and the individual patient evaluation in daily clinical practice.

In conclusion, after 2 years of follow-up female patients still had higher disease activity and worse quality of life and men showed larger OWD and more radiographic damage. Importantly, although female patients switched more often between TNF-α inhibitors, short-term (3 months) and long-term (2 years) change in clinical assessments (including disease activity) was comparable between genders, except men showed more radiographic progression after 2 years than women.

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## Declarations of interest

None.

## Supplementary materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2018.07.015.

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