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Disease activity in women with ankylosing spondylitis remains higher under Tumour Necrosis Factor inhibitor treatment than in men: a five-year observational study

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Objective: To assess sex differences in response, level of disease activity, and drug survival in tumour necrosis factor inhibitor (TNFi)-naïve ankylosing spondylitis (AS) patients.

Method: Consecutive AS patients, fulfilling the modified New York criteria, were included in a prospective cohort study at initiation of the first TNFi and followed until this medication was stopped (drug survival). Disease activity scores [AS Disease Activity Score using C-reactive protein (ASDAS-CRP), Bath AS Disease Activity Index (BASDAI), and CRP] were measured at 3, 6, and 12 months, and every subsequent year, up to 5 years. The response was defined by the ASDAS-CRP response criteria (clinically important improvement: ASDAS-CRP decrease ≥ 1.1). Analyses included regression methods for repeated measurements and survival analyses.

Results: Overall, 356 patients were included (34% women, mean ± sd age 46 ± 12 years), with a median disease duration of 12 (interquartile range 6;20) years. Women were less likely than men to achieve a clinically important response after 6 months of TNFi treatment (47% vs 64%; relative risk 1.4, 95% confidence interval (CI) 1.1;1.9, p = 0.02], despite a lack of sex differences in mean ASDAS-CRP levels over 5 year follow-up. Adjusted models for BASDAI over 5 years showed that women had a 0.6 point higher BASDAI score than men (β = 0.6 0.1;1.1 <0.02). Numerically, more women than men discontinued treatment over a period of 5 years (hazard ratio = 1.5, 95% CI 0.9;2.5, p = 0.15).

Conclusion: Female AS patients show a lower response to TNFi and a higher disease activity compared to men.

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease which can be divided into non-radiographic axSpA (nr-axSpA) and radiographic axSpA [or ankylosing spondylitis (AS)] (1). This study focuses on radiographic axSpA (AS) patients only. AS starts at a young age (15–40 years) and more often affects men than women (in a 3:1 ratio) (2).

Like many other medical treatments, the efficacy of tumour necrosis factor inhibitor (TNFi) has not been fully assessed for sex differences within the AS population, despite accumulating data on gender differences in physiological processes, such as renal and liver function and body composition, which may influence drug metabolism (3). In AS, our group previously documented significant sex differences in TNFi response in another patient population, both in efficacy and in time on drug (4, 5). Two review articles have confirmed that studies on sex differences in AS are limited in number and have a short period of observation (6, 7).

So far, only a few studies have focused on longitudinal follow-up of sex differences in TNFi response in AS, and only two studies had a long follow-up period, with a maximum of 10 years (5, 8, 9).

The primary aim of this study was to analyse sex differences in AS response to the first TNFi after 6 months, in TNFi-naive AS patients. The secondary aims were to assess sex differences in levels of disease activity and drug survival of TNFi over a 5 year follow-up period.

Method

Consecutive patients diagnosed with radiographic axSpA [according to the modified New York criteria (10)], who had started their first TNFi, were included from the outpatient clinics of the VU University Medical Centre and Reade (Amsterdam, Netherlands). All

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data were registered in the Amsterdam Spondyloarthritis (AmSpA) cohort. Patients who had been previously treated with biologicals were excluded.

The study was initiated in January 2000 and included data on AS patients who started with infliximab, adalimumab, etanercept, or golimumab up to June 2018; data collection continued until December 2018. Patients on certolizumab were not included in this study because of the low number of patients and very limited follow-up data.

The study complied with the Declaration of Helsinki and was approved by the local ethics committees of the participating hospitals (approval number NL13486.029.06), and written informed consent was obtained from all participants before inclusion.

All included patients visited the outpatient clinic for screening at baseline (just before the start of TNFi treatment), at 3, 6, and 12 months, and every successive year up to 5 years' follow-up, after the start of the TNFi. In case of incomplete data during the 5 year follow-up, the corresponding reasons for missing data were reported. For patients who were lost to follow-up, additional information on drug status was retrieved from the patient files of the hospitals.

At baseline, demographics, medical history [i.e. year of AS diagnosis and disease onset (first symptoms)] and data on extra-articular manifestations (EAM) (uveitis, psoriasis, and inflammatory bowel disease) were collected.

Blood samples were obtained to determine the presence of the human leucocyte antigen B27 (HLA-B27) (baseline only), the level of acute-phase reactants, C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR) (at every visit). Data on disease activity and function were obtained at every visit through validated questionnaires [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Global score (BASG), on pain and overall well-being through a numerical rating scale]. A physical examination was performed at every visit to assess the Bath Ankylosing Spondylitis Metrology Index (BASMI) and the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).

Disease activity was assessed at every visit with the BASDAI and the Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP). The definitions of the ASDAS-CRP clinical response are: 'clinically important improvement' (CII), with a decrease in the ASDAS ≥ 1.1 and 'major improvement' (MI) in the case of an ASDAS decrease ≥ 2.0, compared to baseline (11–13). In addition, the Assessment SpondyloArthritis international Society (ASAS) 20% and 40% response criteria were analysed (12, 13).

Drug survival was defined as the duration of treatment with the first TNFi, in months. Reasons for treatment discontinuation were treatment related [classified as adverse events (AEs); lack or loss of efficacy (LOE); low disease activity] or non-treatment related (pregnancy; other). Reasons for early censoring included loss to follow-up because of changing hospital, relocation, and lack of further follow-up data. In the case of missing follow-up data, an effort was made to retrieve data on TNFi status from the patient files of the participating hospitals.

Statistical analysis

All data from the AmSpA cohort and the corresponding patients records from January 2000 to December 2018 were used for the analysis. In the case of missed visits, if continued use of the TNFi was documented in the patient record and the interval period between two visits was < 6 months, the first results after the interval were used in the analysis. If the interval was ≥ 6 months, or if there was reasonable doubt over continued treatment during the interval, only the data before the interval were used in the analysis (n = 20).

Demographic data at baseline were analysed cross-sectionally for possible sex differences, with chi-squared and Student's t-tests. Data were presented as mean ± standard deviation (sd) in the case of normally distributed outcomes, or median and interquartile range (IQR) in the case of skewed data. No distinction was made between different TNFi, since they are assumed to be equally efficacious in AS (14–17).

To assess sex differences in TNFi response according to the ASAS response criteria for ASDAS-CRP (CII), Student's t-tests, chi-squared tests, and longitudinal and linear regression analyses were performed.

To assess sex differences in disease status on TNFi treatment at several time points over a 5 year follow-up period, the mean ASDAS-CRP, BASDAI, BASMI, and BASFI values were analysed with the generalized estimating equation (GEE) analysis for sex to correct for repeated measurements over time in one patient. Post hoc, the 5 year mean of each of the six BASDAI questions was analysed with GEE, to investigate which of the components caused the sex differences. A regression coefficient (β) with 95% confidence interval (CI) expressed the difference in mean disease activity value between women and men over time. Age, disease duration, body mass index (BMI), pain, MASES, and CRP (except for ASDAS-CRP) at baseline were assessed as possible confounders in all the aforementioned outcome measures (checked for multicollinearity). Correlations between the MASES and BASDAI component 4 were checked with the Pearson correlation score. Continuous confounders were checked for linearity. An interaction term for time was added to the model to examine whether the sex effect was constant over time. If the interaction term was significant ($p < 0.10$), sensitivity analyses were performed.

Sex differences in time on drug were assessed with Kaplan–Meier survival curves and Cox regression analysis. The start date was defined as the date of the first

injection with a TNFi and the stop date as the last known date that the patient used the (first) TNFi. If a patient switched treatment to another TNFi, only data before the switch were used in the analysis.

Statistical analysis was conducted using SPSS version 26. All statistical tests were two sided, with a p-value of < 0.05 indicating statistical significance. No adjustment was made for multiple testing.

Results

In total, 385 patients with AS were eligible for the study, of whom 29 (8%) were excluded since they were not TNFi naive (n = 25) or their prior treatment status was unknown (n = 4). This resulted in a baseline study population of 356 patients, with a mean ± sd age of 46 ± 12 years, of whom 121 (34%) were women (Table 1), with a mean BMI of 25.9 ± 4.8 kg/m^2. Most patients were HLA-B27 positive, and had long-standing disease and a history of EAM. At baseline, BASDAI was significantly higher, and BASMI significantly lower, in women (Table 1) compared to men.

After 6 months of treatment, 47% of women and 64% of men fulfilled the ASDAS-CRP clinical response criteria of CII (relative risk 1.4, 95%CI 1.1;1.9, p=0.02). The difference was even more prominent at 3 months (46% vs 70%) and extended to both CII and MI. Limited data were available on the ASAS20 response after 3 and 6 months, which was reached by 24.4% (n = 87) and 31.1% (n = 73) of the patients, respectively. After 1 year, no further improvement was observed. No significant gender differences were observed, although the percentage of male ASAS20 responders at 6 months was higher compared to females (31.1% vs 21.5%). At 3 months, only 14.3% (n = 51) fulfilled the ASAS40 criteria. After 3 months of treatment, no additional ASAS40 responders were observed. No sex differences were found in ASAS40 responses.

Over the 5 year follow-up, the mean average BASDAI scores were higher in women than in men (Table 2). The adjusted model (which corrected for the confounders) showed 0.6 (95% CI 0.1;1.1, p = 0.02) higher BASDAI scores in women compared to men (Table 2). Sex differences on BASDAI levels were stable over time. No multicollinearity was observed between age and disease duration (variance inflation factor 1.3).

Table 1. Baseline characteristics of the included patients with ankylosing spondylitis (AS), stratified for sex (N = 356).

Demographic data	Total population (N = 356)	Men (N = 235)	Women (N = 121)
Age (years) (n = 342)	46.4 ± 12.4	47.0 ± 12.2	45.2 ± 13.8
Age at diagnosis (years) (n = 320)	32.1 ± 11.1	32.3 ± 11.7	31.7 ± 10.2
Disease duration (years) (n = 318)	14.3 (6.0;20.3)	12.5 (6.0;21.0)	14.0 (5.0;20.0)
HLA-B27$^+$ (n = 339)	276 (81.7)	178 (80.2)	99 (84.6)
BMI (kg/m^2) (n = 335)	25.9 ± 4.8	25.9 (4.4	25.8 (5.5
Extra-articular manifestations (EAM)			
Frequency (n = 354)	269 (76.0)	171 (73.1)	98 (81.7)
Uveitis (n = 350)	101 (28.9)	58 (25.0)	43 (36.4)
Psoriasis (n = 353)	33 (9.3)	21 (9.0)	12 (10.1)
IBD (n = 354)	28 (7.9)	17 (7.3)	11 (9.2)
Concomitant drugs			
NSAIDs	196 (77.2)	121 (71.2)	56 (66.7)
DMARDs	22 (8.7)	14 (8.3)	8 (9.5)
Disease outcome			
ASDAS-CRP (n = 275)	3.5 ± 0.9	3.5 ± 1.0	3.5 ± 0.9
BASDAI* (n = 342)	5.8 ± 1.9	5.6 ± 1.9	6.2 ± 1.9
CRP (mg/L) (n = 327)	7.0 (2.9;20.0)	8.0 (3.0;25.8)	5.0 (2.5;13.0)
ESR (mm/h) (n = 321)	18.0 (6.0;34.0)	16.5 (5.0;34.0)	18.0 (8.5;34.0)
BASMI* (n = 317)	3.4 ± 2.2	3.7 ± 2.3	2.9 ± 1.9
BASFI (n = 318)	5.3 ± 2.4	5.4 ± 2.4	5.3 ± 2.5
MASES (n = 300)	0.5 (0.0;3.0)	0.0 (0.0;2.75)	2.0 (0.0;4.0)
Patient global well-being (VAS) (n = 320)	6.3 ± 2.4	6.3 ± 2.3	6.3 ± 2.6
Patient pain (VAS) (n = 310)	5.7 ± 2.6	5.7 ± 2.6	5.9 ± 2.6

Data are shown as mean ± sd, median (interquartile range), or n (%).
HLA-B27$^+$, presence of human leucocyte antigen B27; BMI, body mass index; IBD, inflammatory bowel disease; NSAID, non-steroidal inflammatory drug; DMARD, disease-modifying anti-rheumatic drug; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Function Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score (0–13); VAS, visual analogue scale.
*$p < 0.05$.

Table 2. Results of generalized estimating equation analyses for sex in mean disease status over time in ankylosing spondylitis.

Baseline to 5 year follow-up	β	95% CI	p
BASDAI			
Crude	0.9	0.4;1.3	< 0.001*
Adjusted	0.6	0.1;1.1	0.02*
ASDAS-CRP			
Crude	0.1	–0.1;0.3	0.3
BASMI			
Crude	–0.8	–1.2;–0.4	< 0.001*
Adjusted	–0.6	–1.2;–0.1	0.03
CRP level			
Crude	–0.2	–0.5;0.0	0.08

Encoded male: 0 and female: 1. All GEE analyses were checked for consistency over time by an effect-modifier check for follow-up time in the final model.
β, regression coefficient; CI, confidence interval; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using C-reactive protein; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein.
*Statistically significant (p < 0.05). BASDAI: disease duration, age, CRP–baseline, pain, body mass index (BMI)–baseline, and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)–baseline. BASMI: age, disease duration, CRP–baseline, pain, BMI–baseline, and MASES–baseline.

Separate analyses of the BASDAI components revealed that all questions showed higher scores in women compared to men, not just the pain scores alone (Table 3). These differences remained after correction for the confounders CRP, disease duration, age, BMI, and MASES. No correlation was observed between the subjective BASDAI question 4 and the objective measurement MASES (Pearson correlation = 0.27).

Additional disease outcome parameters (mean ASDAS-CRP, BASFI, BASMI, and CRP) showed a significant mean improvement after 6 months and remained stable up to 5 years of follow-up (Table 2, Supplement S1). The mean BASMI scores were lower in women than in men (–0.6, 95% CI –1.2;–0.1, $p = 0.03$) at all time-points over a 5 year period (Table 2, Supplement S2). No sex differences were observed in mean ASDAS-CRP, BASFI, and CRP scores.

Patient flow over 5 years of follow-up

A total of 214 patients (60%) remained on their first TNFi for 3 years and 161 patients (45%) for 5 years (Figure 1). The most important reasons for loss to follow-up were LOE (n = 38, 19.5%), AEs (n = 18, 9.2%), and relocation to other hospitals (n = 15, 7.7%) (Figure 1). No differences were observed between men and women: LOE, 21 men (17.9%) vs 15 women (19.2%); AEs, 10.3% vs 11.5%; and other reasons for loss to follow-up, 20 men (17.1%) vs 16 women (20.5%).

Drug survival of the first TNFi

Overall, 131 out of 356 patients (36.8%) were lost to follow-up, of whom 74 patients had no treatment-related reason for dropping out from the cohort (censored) (median treatment duration 32 months, IQR 12;48). Of the remaining patients who had a drug-related reason for dropping out from the cohort (n = 57, 43.5%), median drug survival was 48 months (IQR 13;60). There were no significant sex differences in TNFi survival (women 49 ± 2 vs men 53 ± 1 months) (Figure 2). Numerically, women had an increased risk

Table 3. Overview of the different Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questions, by sex.

Question on BASDAI	Baseline (n = 345)				GEE analyses over 5 years					
					Crude model			Adjusted model		
	M	F	95% CI	p	B	95% CI	p	B	95% CI	p
1. Fatigue	6.6	7.2	–1.1;–0.1	0.05	0.9	0.4;1.4	0.001	0.7	0.1;1.4	0.02
2. Spinal pain	6.9	7.1	–1.1;–0.2	ns	0.8	0.2;1.3	0.004	0.6	0.01;1.2	0.05
3. Joint involvement	4.3	4.7	–1.1;0.3	ns	0.8	0.3;1.4	0.002	0.4	–0.2;1.1	0.18
4. Discomfort after pressure	5.2	5.6	–1.8;1.0	ns	0.9	0.2;1.6	0.01	0.9	0.2;1.5	0.01
5. Morning stiffness	6.7	6.8	–0.7;0.4	ns	0.7	0.2;1.2	0.01	0.4	–2.0;1.0	0.18
6. Duration of morning stiffness	5.6	5.7	–0.9;0.5	ns	0.4	–0.1;1.0	0.1	0.2	–0.5;0.8	0.57

A significant difference is defined as p < 0.05; ns, non-significant.
BASDAI scale: 0–10; GEE, generalized estimating equation; M, male; F, female; CI, confidence interval; β, regression coefficient. All components were checked for the following confounders: disease duration, age, C-reactive protein–baseline, pain, body mass index, and Maastricht Ankylosing Spondylitis Enthesitis Score. All GEE analyses were checked for consistency over time by an effect-modifier check for follow-up time in the final model.

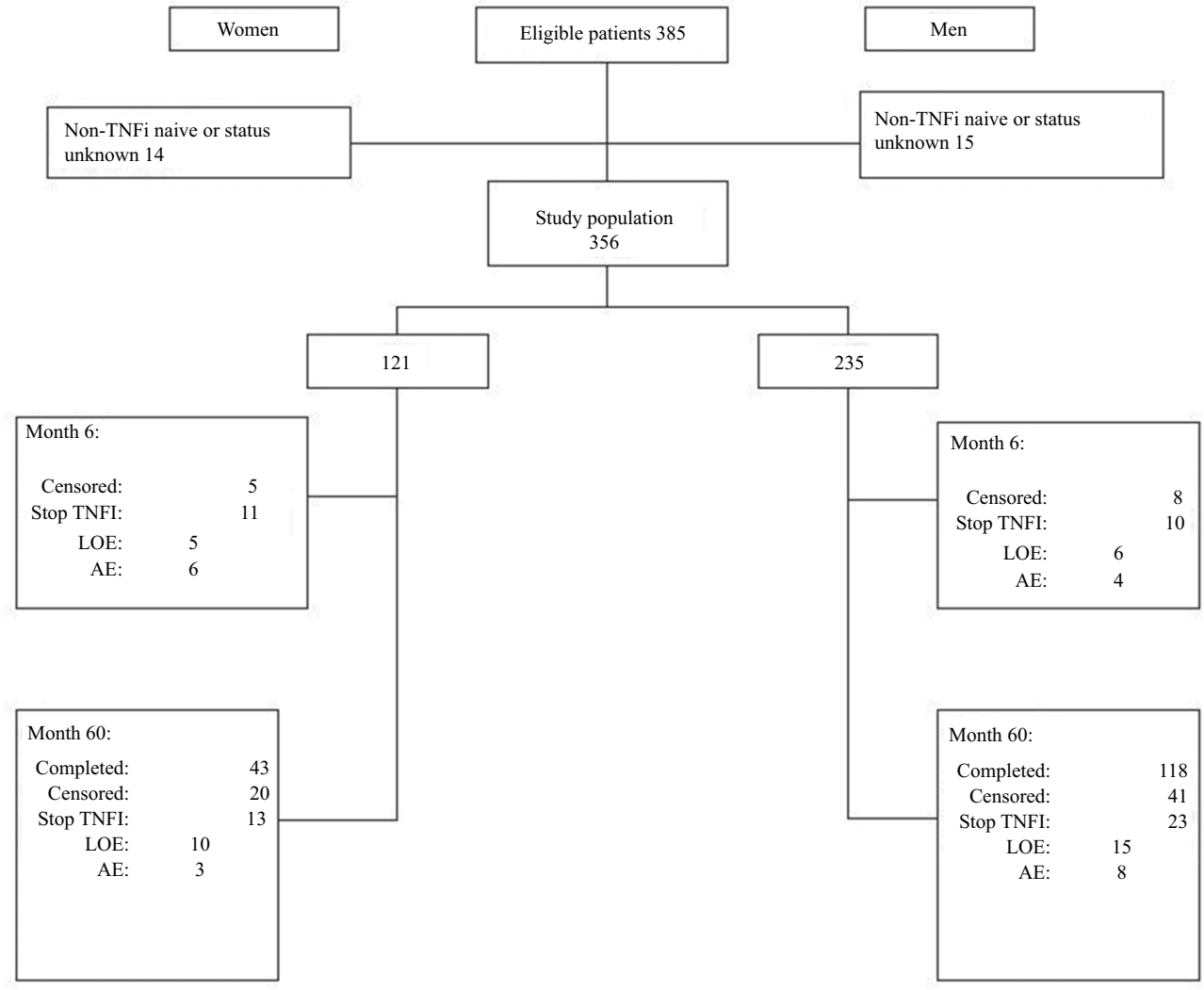

Figure 1. Flowchart of data availability over 5 years for patients in the Amsterdam Spondyloarthritis (AmSpA) cohort (N = 356). TNFi, tumour necrosis factor inhibitor; LOE, lack or loss of efficacy; AE, adverse event; censored, patients who were lost to follow-up without known treatment discontinuation.

for TNFi discontinuation [hazard ratio (HR) 1.5, 95% CI 0.9;2.5, p = 0.15] compared to men.

Discussion

In this cohort of AS patients initiating TNFi treatment, women showed less response and overall higher disease activity in long-term follow-up. Although drug survival in months was similar between both sexes, women showed a numerically a higher likelihood of drug discontinuation compared to men.

Our observations confirm previous studies that revealed an average 20% difference in response rates between women and men in ASDAS-CRP response (4, 18). In addition, this study revealed a substantial sex difference in a longitudinal analyses for the disease activity score BASDAI. It has been hypothesized that

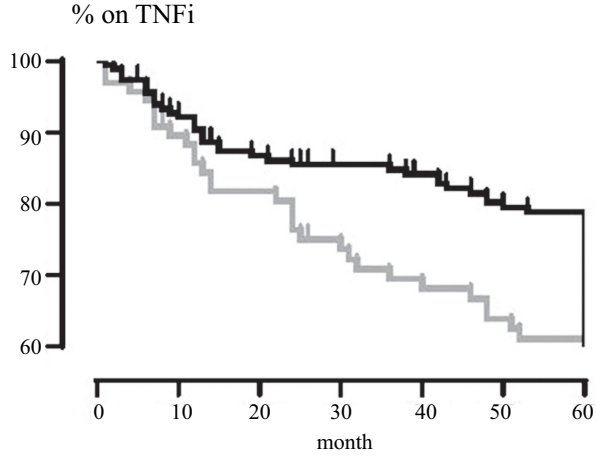

Figure 2. Time (in months) on the first tumour necrosis factor inhibitor (TNFi), by sex. Grey line, women; black line, men.

women have, on average, higher BASDAI scores, mainly owing to higher levels of reported pain, but this study demonstrates higher values of all BASDAI components in women compared to men, not only pain. These elevated scores of BASDAI components in women correspond with the findings of one other study and additionally with results of the early stages of the disease (19). Of note, that study also included patients diagnosed with psoriatic arthritis and nr-axSpA and only cross-sectional analyses were performed instead of the longitudinal analyses in our study (20).

Reduced drug survival in women on TNFi was also described in two reviews (12, 13) describing one study including 122 comparable axSpA patients in a peripheral clinical setting (5). In our study, women had a numerically, but not significantly, higher risk (HR 1.5) than men of discontinuing their first TNFi treatment over a period of 5 years. Taking into account the relatively low number of patients included in the drug survival analysis (n = 57), this may be a reasonable explanation for not finding a significant difference in drug survival between men and women.

Our study substantially contributes to the scarce literature on sex differences in TNFi response in AS because data were analysed at several time points in daily clinical practice over such a long follow-up period. Only two studies (both by Glintborg et al) assessed data over comparable follow-up periods, but they used survival curves and logistic regression analyses (8, 9) and no longitudinal regression analyses such as GEE. These two studies found comparable results considering sex differences. In addition, only three studies included a larger study population than our study (440, 603, and 1283 vs 356) (4, 9, 18). However, one of these studies included pooled data from several randomized controlled trials, which is different from our prospective observational cohort design.

Possible explanations for sex differences in treatment efficacy include differences in drug metabolism, owing to differences in renal and hepatic function, weight, length, and body composition (3). It has also been suggested that the higher proportion of body fat in women increases the levels of TNF-α and decreases the efficacy of TNFi (21). The lack of sex differences in mean average ASDAS-CRP scores may be explained by the higher CRP levels in men which raise the ASDAS-CRP values, whereas the other ASDAS components, such as back pain, peripheral pain, and duration of morning stiffness, are higher in women. An alternative hypothesis suggests that women are more likely to suffer from widespread pain than men (22). However, this study revealed no higher global pain scores in women (mean ± sd 5.9 ± 2.6) compared to men (5.7 ± 2.6). Improvement of function (BASFI) and BASMI after the start of TNFi was comparable between the two sexes, although the BASMI scores remained higher in men with AS compared to women, which corresponds with other studies (9, 23, 24).

Our study has a few limitations. Only AS patients who fulfilled the modified New York criteria were included in this study, which could be seen as a limitation, since TNFi are not limited as treatment for this axSpA subgroup. However, we believe that our study results showed a reliable overview of AS patients in clinical practice, which is in our opinion a valuable addition to already existing data. As with any observational study, missing data and loss to follow-up increase the risk of bias. Loss to follow-up occurred similarly in women and men, which, in our opinion, did not compromise the results. GEE analyses were used in this study to handle the missing data and strengthen our longitudinal findings on disease activity levels and the observed differences between men and women by calculating the mean of the disease activity scores over all the follow-up measurements, which we checked in the final GEE model for consistency over time by adding an interaction term for follow-up time to the model (25).

Another possible weakness could be the selection bias at inclusion, since we have no insight into whether every eligible patient was approached for possible study inclusion. However, our demographic data correspond very well with the patient populations of the previous studies, and thus were directly comparable.

Conclusion

This cohort study demonstrates a higher disease activity and lower response rate to TNFi in women with AS than in men. We suggest that more sex-specific treatment strategies in AS should be developed to optimize treatment for both sexes.

Disclosure statement

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Supplementary material

Supplemental data for this article can be accessed here.