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ORIGINAL RESEARCH

Sex differences in the effectiveness of first-line tumour necrosis factor inhibitors in axial spondyloarthritis: results from the EuroSpA Research Collaboration Network

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ABSTRACT

Objective Evidence indicates reduced treatment effectiveness of TNFi in women with axial spondyloarthritis (axSpA) compared with men. We aimed to investigate sex differences in treatment response and retention rates over 24 months of follow-up in axSpA patients initiating their first TNFi.

Methods Data from axSpA patients initiating a TNFi in 1 of 15 registries within EuroSpA collaboration were pooled. We investigated the association of sex with treatment response using logistic regression. The primary outcome was clinically important improvement (CII) at 6 months according to Ankylosing Spondylitis Disease Activity Score with C-reactive protein (CRP) (≥1.1 decrease). We adjusted for age, country and TNFi start year. A secondary outcome was retention rates over 24 months of follow-up assessed by Kaplan-Meier estimator.

Results In total, 6451 axSpA patients with data on CII were assessed for treatment response; 2538 (39%) were women and 3913 (61%) were men. Women presented at baseline with lower CRP levels but had higher scores on patient-reported outcome measures. At 6 months, 53% of the women and 66% of the men had CII. Women had a lower relative risk of CII compared with men (0.81; 95% CI 0.77 to 0.84). This sex difference was similar in adjusted analysis (0.85; 95% CI 0.82 to 0.88). Retention rates were evaluated in 27 702 patients. The TNFi 6/12/24 months retention rates were significantly lower among women (79%/66%/53%) than men (88%/79%/69%).

Conclusion Treatment response and retention rates are lower among women with axSpA initiating their first TNFi. Sex differences in treatment effectiveness were present regardless of the outcome measure used for treatment response, and differences in retention rates transpired early and increased as time progressed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research has identified sex differences in the manifestation and course of axial spondyloarthritis (axSpA), as well as differences in gene expression, immunological factors, body composition and pharmacokinetic variables. These differences may impact a wide range of outcomes.

⇒ Previous studies have also found that women tend to have reduced treatment effectiveness with TNFi compared with men.

BACKGROUND

Spondyloarthritis (SpA) can be classified as axial SpA (axSpA) when predominantly involving the axial skeleton, including the sacroiliac joints, or as peripheral SpA with predominantly peripheral arthritis, dactylitis and enthesitis.[1] AxSpA can be further divided into radiographic axSpA (r-axSpA) (i.e., ankylosing spondylitis), with definite radiographic signs of sacroiliitis and non-radiographic axSpA (nr-axSpA).[2] Interestingly, the sex distribution is different in these subtypes. In r-axSpA, most patients are men (75%), whereas the sex distribution is equal in nr-axSpA.[3 4]

Numerous studies have observed significant sex differences in the manifestation and course of axSpA. Women with axSpA tend to present with more peripheral complaints, a

WHAT THIS STUDY ADDS

⇒ This is the first study to quantify sex differences in treatment response and retention rates in a large, multinational population.

⇒ The results of this study demonstrate that sex differences in treatment effectiveness are consistent and present in patients with radiographic and non-radiographic axial spondyloarthritis.

⇒ The study findings indicate that the impact of sex on retention rates in patients treated with TNFi appears to become more pronounced over time rather than being a transient effect.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings emphasise the importance of taking sex differences into account when treating patients with axSpA. Improved awareness of these differences is needed in clinical practice and research.

⇒ It is unclear whether sex-tailored treatment strategies are feasible or effective, and further research in this area is necessary.

higher prevalence of thoracic pain and widespread pain, and experience worse functional limitations and quality of life than men. In contrast, men with axSpA are more likely to have objective signs of inflammation, including higher levels of C-reactive protein (CRP), and more frequent radiographic damage, both at presentation and in terms of development over time.[4–7] In addition to these clinical sex differences, sex differences have been observed in factors such as gene expression, immunological factors, body composition and pharmacokinetics, which can impact the effectiveness of treatment.[4 8–10] This emphasises the need to consider sex when evaluating treatment response in axSpA research to ensure that the results of such studies accurately reflect the experiences of both men and women.

Women with axSpA may have reduced treatment effectiveness of tumour necrosis factor inhibitors (TNFi) compared with men,[4 5] as demonstrated in several observational studies.[11–19] However, these studies have limitations, such as a lack of nr-axSpA patients[11 13 14 16 17 19] and relatively small sample sizes.[11 12 14–19] Moreover, treatment effects were not stratified by sex.[11 14 16]

The European SpA (EuroSpA) Research Collaboration Network is a scientific collaboration of 16 European registries that aims to enhance research in real-life clinical practice in SpA patients. In this study, we aimed to investigate sex differences in treatment response and retention rates over 24 months of follow-up among axSpA patients initiating their first TNFi.

METHODS

The EuroSpA Research Collaboration Network

In this study, anonymised data from patients registered with a diagnosis of axSpA initiating their first TNFi in 1 of the following 15 registries were analysed: SCQM (Switzerland), ATTRA (Czech Republic), DANBIO (Denmark), ICEBIO (Iceland), GISEA (Italy), AmSpA (Netherlands), NOR-DMARD (Norway), Reuma.pt (Portugal), RRBR (Romania), SRQ (Sweden), ROB-FIN (Finland), biorx.si (Slovenia), BIOBADASER (Spain), TURKBIO (Turkey), BSRBR-AS (UK). The initiation of data collection occurred between 1999 and 2013 for the different registries, and the data included in this study were collected until 2020.

Study design

The individual registries collected data prospectively according to their respective protocols. In this study, we analysed the data retrospectively. The variables included in this study were predefined in the study protocol.

Patients

All patients with a clinical diagnosis of axSpA were included in the study if they met the following criteria:

- Aged 18 years or older at time of treatment initiation.
- Biologic-naive.
- Treated with their first TNFi.

For the primary analysis of treatment response (primary cohort), data from patients with available Ankylosing Spondylitis Disease Activity Score (ASDAS) scores at baseline and 6 months were used. Patients with available data on secondary outcome measures at 6, 12 or 24 months were included in the secondary analysis of treatment response (secondary cohorts), and those with available data on retention rates (retention cohort) were included in the retention analysis.

Clinical variables

The sex of the patients was reported as 'female' or 'male' according to the protocol of the respective registry. The gender identity of the patient was unknown. However, for readability purposes, we will refer to patients as 'men' or 'women' in this paper.

Baseline characteristics included: age, country, fulfilment of Assessment of SpondyloArthritis international Society (ASAS) classification criteria, fulfilment of modified New York criteria (mNYc), subtype of axSpA (classified as r-axSpA if fulfilling the mNYc and nr-axSpA if fulfilling the ASAS criteria but not mNYc), disease duration defined as years since symptoms onset, smoking status (ie, current, never or former), type of TNFi used, start year of TNFi, Human Leucocyte Antigen B27 (HLA-B27) status and concurrent treatment with non-steroidal anti-inflammatory drugs (NSAIDs). The clinical variables arthritis (ever or never), enthesitis (ever or never), 28-swollen joint count, 28-tender joint count, Bath Ankylosing Spondylitis Functional Index (BASFI) (Visual Analogue Scale (VAS) 0–100 mm), CRP, body mass index (kg/m^2), patient's global assessment (VAS 0–100 mm), patient's pain (VAS 0–100 mm) and fatigue score (VAS 0–100 mm) were also collected.

Outcome measures

Treatment response was based on disease activity, assessed at baseline and after 6 (range, days 151–270), 12 (271–545) and 24 (546–910) months of follow-up.

The primary outcome was treatment response at 6 months of follow-up, evaluated by ASDAS-CRP clinically important improvement (CII). An ASDAS-CRP CII was defined as a decrease of ≥1.1 in the ASDAS-CRP score from baseline.[20] CII at 12 and 24 months were considered secondary outcomes.

Other secondary outcomes were evaluated at 6, 12 and 24 months and included: ASDAS-CRP major improvement (MI) (≥2.0 points), inactive disease (ID) (≤1.3) and low disease activity (LDA) (≤ 2.1), achievement of 20%/40% improvement in the ASAS response criteria (ASAS20/40), defined as at least 20% or 40% improvement, respectively, in at least three of the four domains: patient global assessment, pain, function and inflammation, with no worsening in the remaining domain,[21] Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[22] remission (<20) and LDA (<40), and 50% improvement of the BASDAI (BASDAI50).

Furthermore, retention rates were defined as the time from treatment initiation to discontinuation from any cause. If no registered stop date was available, observations were censored at the last time point with available clinical data (either 6, 12 or 24 months) and at study termination, that is, after 24 months of follow-up.

Statistical analysis

Data were pooled across all countries. The R V.3.6.3 software (www.r-project.org) was used for the statistical analyses. Descriptive statistics (mean, SD, median, IQR or percentages) were performed for demographics and patient characteristics.

Treatment response

The association between sex and treatment response was assessed using logistic regression. Important covariates influencing the outcomes were determined a priori in the statistical analysis plan and selected based on availability in the pooled dataset. All covariates with more than 20% missing values, in addition to smoking status, and ever use of conventional synthetic disease-modifying antirheumatic drugs, were excluded. The final covariates included in the model were age, country and TNFi start year. We applied the logistic regression model to predict the mean probability of response in both the female (P_1) and male (P_0) populations. From these probabilities, we calculated the relative risk (RR) (P_1/P_0) and the risk difference (RD) ($P_1–P_0$). To achieve valid confidence intervals, we performed bootstrap iterations (1000 resamples). The unadjusted and adjusted effects were evaluated for all outcomes (ie, disease activity scores and response criteria) at 6, 12 and 24 months.

In the primary analysis, subgroup effects for country, subtype of axSpA (ie, r-axSpA and nr-axSpA), and calendar periods 1999–2008, 2009–2014 and 2015–2020 were investigated. The calendar period cut-off values were selected in concordance with a previous study within the EuroSpA collaboration.[23] Sensitivity analyses were performed to adjust for arthritis or enthesitis, or both conditions, HLA-B27, disease duration and concomitant NSAID in patients with available data. Changes in the components of the ASDAS (baseline vs 6 months), stratified by sex, were assessed using descriptive statistics.

Retention to treatment

Retention rates pooled and stratified per country were estimated using the Kaplan-Meier estimator for both sexes. Differences were tested with the log-rank test. Cox proportional-hazards models were used to estimate a weighted average of the HRs (women vs men) for treatment discontinuation of a TNFi over 24 months of follow-up. The adjusted models included the same covariates as the rest of the analyses. The Schoenfeld residual test was performed to assess the proportional hazards assumption. Possible violations were further inspected visually (residual plots, log-log plots) and resolved through stratification in the Cox regression model if appropriate. The analyses were also stratified for the same calendar periods described above.

Missing data due to drop-outs in the treatment response group (primary cohort)

Compared with the proportion of patients with available data for retention analysis, the proportion of patients with data on treatment response was low. We assumed these data were missing completely at random and performed a complete-case analysis. To confirm this assumption, we assessed disparities in baseline characteristics among patients with retention rate data and those with available ASDAS-CRP CII at 6 months.

Threshold values for statistical significance

All comparisons were conducted with a two-sided test. The threshold value for statistical significance was 0.05 in the primary and retention analyses. For the secondary outcomes, a more stringent threshold value of 0.00092 was used to account for multiple comparisons. This value was derived by dividing 0.05 by the total of 54 tests conducted, which takes into account nine secondary outcomes, 3 time points, and both unadjusted and adjusted effects, ultimately resulting in a total of 54 tests.

RESULTS

In the 15 EuroSpA registries, 28 616 patients started their first TNFi treatment. Of these, 6451 (39% women) with available baseline and 6 months ASDAS scores formed the primary cohort for treatment response analysis, while 27 702 (40% women) patients were included in the retention analysis. For additional details, please see figure 1.

Patient characteristics at baseline

Primary cohort

Baseline characteristics, including the percentage of participants with missing data, are presented in table 1. Overall, notable differences existed between the sexes at baseline. Women had more frequently ‘ever’ enthesitis (21% vs 15%). In comparison, men were more often

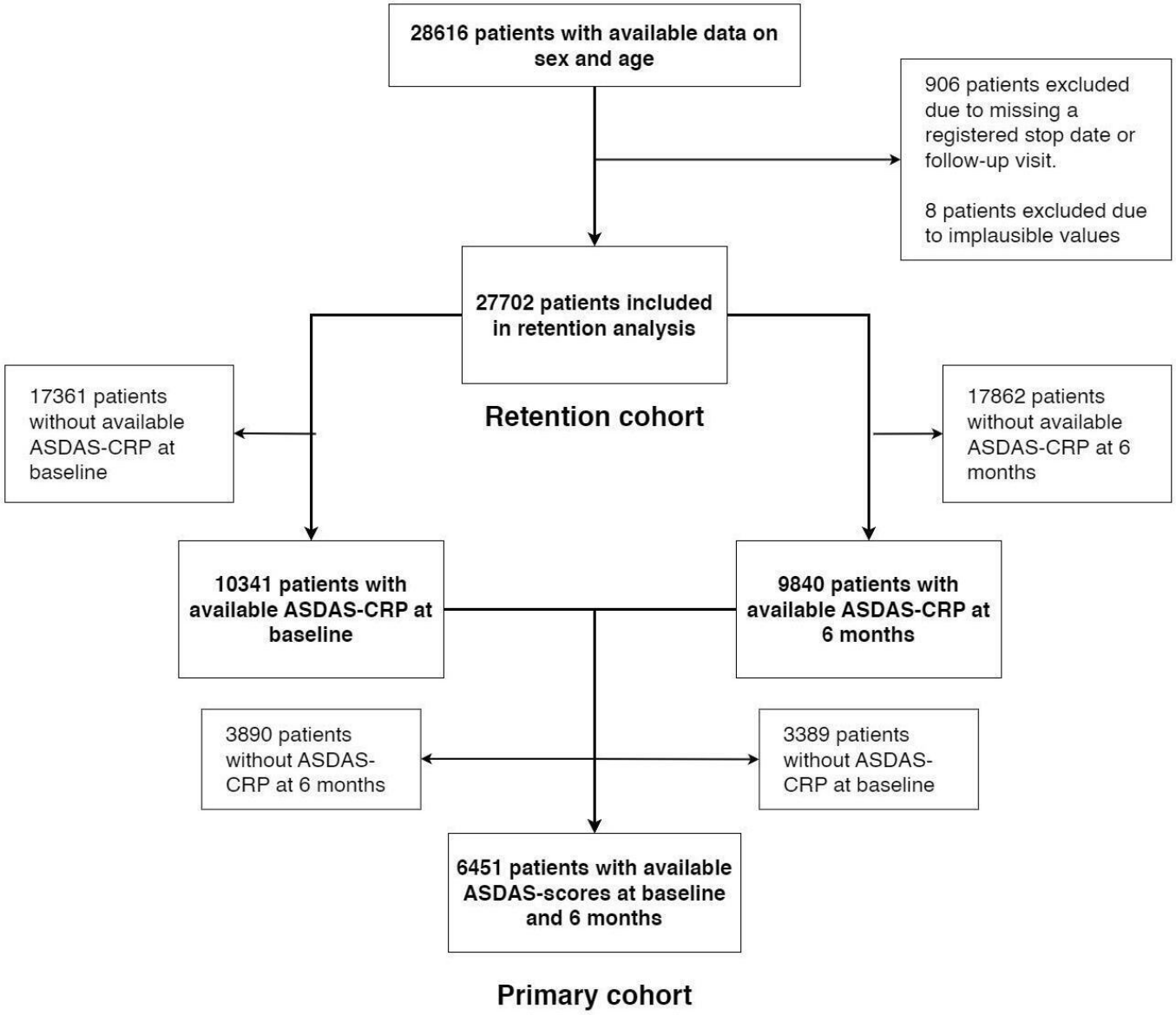

Figure 1 Flow chart illustrating the inclusion of study participants for the primary cohort and retention cohort analyses. All participants were biologic-naïve and received their first tumour necrosis factor inhibitor treatment. ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive protein.

HLA-B27 positive (83% vs 72%), current smokers (31% vs 22%) and had more frequently elevated CRP levels (>10 mg/L, 56% vs 40%). Women reported slightly higher scores on patient-reported outcome measures, including BASDAI, BASFI, VAS pain and VAS fatigue.

Only a limited number of data were available on the classification of axSpA as r-axSpA and nr-axSpA (N=1576, 24%). However, women were more commonly classified as nr-axSpA compared with men (31% vs 19%). Baseline characteristics of patients with r-axSpA and nr-axSpA, stratified by sex, are present in online supplemental table S1.

Retention cohort

Baseline characteristics of the study population used for retention analyses with available data on age, sex and retention rates are presented in table 2. The women in the primary cohort were mainly similar to those in the retention cohort. Two notable differences existed. Women in the primary cohort reported enthesitis less often (21% vs 31%) and less frequently started their TNFi in 1999–2008 (4.5% vs 18%) than women included in the retention cohort. Similar differences existed between men included in the primary cohort and retention cohort.

Treatment response

Primary cohort

The probability for women to have CII was 19% (unadjusted RR 0.81; 95% CI 0.77 to 0.84) lower than men, and the difference in probability of having CII was 13 percentage points (unadjusted RD 0.13; 95% CI 0.10 to 0.15). The adjusted analysis revealed similar differences (RR 0.85, 95% CI 0.82 to 0.88; RD 0.097, 95% CI 0.074 to 0.12) (table 3). Compared with

Table 1 Baseline characteristics and standardised mean differences (SMD) of patients with axSpA initiating their first TNFi, with available ASDAS-CRP at baseline and 6 months

	Women (n=2538)			Men (n=3913)			SMD
	Pct. missing	Value		Pct. missing	Value		
Patient characteristics							
Age, years—mean (SD)	0	42.0	(12.1)	0	41.4	(12.3)	0.049
Subtype nr-axSpA*—no (%)	76	187	(31)	75	185	(19)	0.288
HLA-B27 positive—no (%)	47	956	(72)	41	1932	(83)	0.277
Disease duration, years—median (IQR)	20	8	(3–16)	21	10	(4–18)	0.160
TNFi—no (%)	0			0			0.078
Infliximab		532	(21)		863	(22)	
Etanercept		606	(24)		914	(23)	
Adalimumab		743	(29)		1199	(31)	
Certolizumab		224	(8.8)		270	(6.9)	
Golimumab		433	(17)		667	(17)	
Smoking status—no (%)	9			9			0.244
Current		516	(22)		1095	(31)	
Never		1309	(57)		1590	(45)	
Former		494	(21)		861	(24)	
BMI, kg/m^2—mean (SD)	58	26.7	(5.7)	51	26.6	(4.8)	0.013
Cohort characteristics—no (%)							
TNFi start year	0			0			0.121
1999–2008		115	(4.5)		276	(7.1)	
2009–2014		1013	(40)		1620	(41)	
2015–2020		1410	(56)		2017	(52)	
Country	0			0			0.286
Switzerland		78	(3.1)		90	(2.3)	
Czech Republic		318	(13)		807	(21)	
Denmark		514	(20)		737	(19)	
Iceland		9	(0.4)		16	(0.4)	
Netherlands		47	(1.9)		98	(2.5)	
Norway		339	(13)		551	(14)	
Portugal		269	(11)		287	(7.3)	
Romania		56	(2.2)		132	(3.4)	
Sweden		466	(18)		548	(14)	
Finland		56	(2.2)		87	(2.2)	
Slovenia		48	(1.9)		51	(1.3)	
Turkey		279	(11)		384	(9.8)	
UK		59	(2.3)		125	(3.2)	
Disease manifestations							
Arthritis (ever)—no (%)	70	312	(40)	71	425	(37)	0.072
Enthesitis (ever)—no (%)	61	210	(21)	53	279	(15)	0.149
Disease activity							
ASDAS, units—mean (SD)	0	3.5	(0.9)	0	3.5	(1.0)	0.072
BASDAI, mm—mean (SD)	1	59	(20)	2	54	(21)	0.238
BASFI, mm—mean (SD)	19	48	(25)	21	46	(24)	0.106

Continued

Table 1 Continued

	Women (n=2538)			Men (n=3913)			SMD
	Pct. missing	Value		Pct. missing	Value		
CRP (mg/L)—median (IQR)	0	7	(3–16)	0	12	(4–25)	0.284
CRP>10 mg/L—no (%)	0	1008	(40)	0	2196	(56)	0.333
SJC (0–28)—median (IQR)	38	0	(0–0)	45	0	(0–0)	0.153
TJC (0–28)—median (IQR)	41	0	(0–2)	47	0	(0–1)	0.248
Patient pain assessment, mm—mean (SD)	11	63	(22)	8	59	(24)	0.181
Patient fatigue assessment, mm—mean (SD)	20	65	(25)	17	59	(26)	0.272
Patient global assessment, mm—mean (SD)	0	65	(23)	0	61	(23)	0.163

SMDs are provided to quantify the differences between women and men. An SMD close to 0 suggests negligible differences, whereas values of 0.2, 0.5 and 0.8 were considered to represent small, moderate and large differences, respectively.
*Patients registered to fulfil the ASAS criteria for axSpA and not to fulfil the modified New York criteria (nr-axSpA) or patients registered as fulfilling the modified New York criteria (r-axSpA).
ASAS, Assessment in SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; AxSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; CRP, C-reactive protein; HLA-B27, human leukocyte antigen B27; nr-axSpA, non-radiographic axSpA; Pct., percentage; r-axSpA, radiographic axSpA; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor.

men, women had overall diminished improvement in all components, especially in spinal pain, patient global assessment and CRP (online supplemental table S2).

Subgroup and sensitivity analyses

We stratified the analyses by country and observed comparable effects in CII, that is, a reduced response probability in women. However, countries with few study participants and the registry ATTRA (Czech Republic) showed a similar trend but failed to demonstrate a statistically significant difference (table 3). We evaluated whether the period in which TNFi treatment was initiated influenced our results. Similar significant effects as in the primary analysis were observed for CII only in 2009–2014 and 2015–2020 (online supplemental table S3). Moreover, we compared patients classified as nr-axSpA with r-axSpA and discovered significant effects of sex on CII in both subtypes (online supplemental table S4). Additional sensitivity analyses revealed similar adjusted effects when arthritis, enthesitis, concomitant NSAIDs, disease duration and HLA-B27 were added to the covariates used in the primary analysis, available in online supplemental table S5.

Secondary cohorts

Evaluation of other disease activity scores revealed similar results at 6 months, 12 months and 24 months (table 4). However, overall, the effect sizes diminished over time, and the percentage of women in the analyses dwindled towards the end of the follow-up period (data not shown). Notably, at 6 months, we observed the most significant effects in ASDAS-CRP ID (unadjusted RR 0.66; 95% CI 0.61 to 0.71) and the smallest in ASAS40 response (0.82; 95% CI 0.76 to 0.88). RDs for the secondary outcomes are available in online supplemental table S6.

Treatment adherence

Retention cohort analysis

During the follow-up period of 24 months, 8934 (32%) of the 27 702 patients included in the retention cohort discontinued their first TNFi. Women had lower retention rates at all time points, and these differences were significant (p<0.001, log-rank test). The retention rates at 6, 12 and 24 months were 79% (95% CI 79% to 80%), 66% (95% CI 65% to 67%) and 53% (95% CI 52% to 54%) for women, and 88% (95% CI 88% to 89%), 79% (95% CI 79% to 80%) and 69% (95% CI 68% to 70%) for men, respectively. Figure 2 shows retention rates for men and women for up to 2 years of follow-up, estimated with the Kaplan-Meier estimator. In the subgroup analyses of the individual countries, similar results were observed as in the pooled analysis; although in 3 out of 15 registries, the difference in retention rates did not reach the threshold for significance (figure 3).

Risk for treatment discontinuation of TNFi

Over a follow-up period of 24 months, 27 702 patients were included in the Cox regression analyses. In the unadjusted analysis, women's risk for treatment discontinuation of a TNFi was 71% higher than men's (HR 1.71; 95% CI 1.64 to 1.79). After adjustment, the HR remained significant (1.66, 95% CI 1.59 to 1.73). We evaluated trends across calendar periods and observed small fluctuations in the unadjusted HRs: 1999–2008/2009–2014/2015–2020 (1.57 (95% CI 1.43 to 1.74)/1.77 (95% CI 1.67 to 1.89)/1.65 (95% CI 1.54 to 1.77)). The adjusted analyses yielded similar HRs: 1999–2008/2009–2014/2015–2020 (1.61 (95% CI 1.46 to 1.78)/1.73 (95% CI 1.63 to 1.84)/1.61 (1.51 to 1.73)).

Table 2 Baseline characteristics and standardised mean differences (SMD) of patients with axSpA initiating their first TNFi, with available data on retention rates

	Women (n=11 084)			Men (n=16 618)			SMD
	Pct. missing	Value		Pct. missing	Value		
Patient characteristics							
Age, years—mean (SD)	0	43.1	(12.4)	0	42.2	(12.4)	0.076
Subtype nr-axSpA*—no (%)	81	659	(32)	78	642	(17)	0.334
HLA-B27 positive—no (%)	60	3021	(68)	56	5963	(81)	0.294
Disease duration, years—median (IQR)	30	8	(3–16)	30	10	(4–19)	0.184
TNFi—no (%)	0			0			0.120
Infliximab		2578	(23)		4583	(28)	
Etanercept		3036	(27)		4170	(25)	
Adalimumab		3519	(32)		5191	(31)	
Certolizumab		620	(5.6)		674	(4.1)	
Golimumab		1331	(12)		2000	(12)	
Smoking status—no (%)	20			21			0.193
Current		1787	(20)		3530	(27)	
Never		4939	(55)		6115	(46)	
Former		2188	(25)		3513	(27)	
BMI, kg/m^2—mean (SD)	58	26.4	(5.7)	55	26.5	(4.5)	0.013
Cohort characteristics—no (%)							
TNFi start year	0			0			0.140
1999–2008		1973	(18)		3833	(23)	
2009–2014		4402	(40)		6538	(39)	
2015–2020		4709	(43)		6247	(38)	
Country	0			0			0.241
Switzerland		836	(7.5)		953	(5.7)	
Czech Republic		752	(6.8)		1868	(11)	
Denmark		1507	(14)		2425	(15)	
Spain		263	(2.4)		552	(3.3)	
Iceland		105	(0.9)		184	(1.1)	
Italy		995	(9.0)		1139	(6.9)	
Netherlands		94	(0.8)		184	(1.1)	
Norway		700	(6.3)		1028	(6.2)	
Portugal		609	(5.5)		640	(3.9)	
Romania		180	(1.6)		477	(2.9)	
Sweden		3243	(29)		4471	(27)	
Finland		418	(3.8)		611	(3.7)	
Slovenia		215	(1.9)		330	(2.0)	
Turkey		807	(7.3)		1030	(6.2)	
UK		360	(3.2)		733	(4.4)	
Disease manifestations							
Arthritis (ever)—no (%)	74	1233	(42)	73	1603	(36)	0.121
Enthesitis (ever)—no (%)	73	924	(31)	70	1045	(21)	0.228
Disease activity							
ASDAS, units—mean (SD)	61	3.4	(0.9)	64	3.5	(1.0)	0.073
BASDAI, mm—mean (SD)	46	59	(20)	47	54	(21)	0.220

Continued

Table 2 Continued

	Women (n=11 084)			Men (n=16 618)			SMD
	Pct. missing	Value		Pct. missing	Value		
BASFI, mm—mean (SD)	55	47	(25)	57	45	(25)	0.062
CRP (mg/L)—median (IQR)	34	6	(3–16)	33	12	(5–26)	0.294
CRP>10 mg/L—no (%)	34	2848	(39)	33	6254	(57)	0.353
SJC (0–28)—median (IQR)	50	0	(0–1)	57	0	(0–0)	0.125
TJC (0–28)—median (IQR)	55	1	(0–4)	61	0	(0–2)	0.307
Patient pain assessment, mm—mean (SD)	37	63	(23)	40	58	(24)	0.183
Patient fatigue assessment, mm—mean (SD)	58	65	(25)	60	58	(26)	0.290
Patient global assessment, mm—mean (SD)	0	64	(24)	0	60	(24)	0.176

SMDs are provided to quantify the differences between women and men. An SMD close to 0 suggests negligible differences, whereas values of 0.2, 0.5 and 0.8 were considered to represent small, moderate and large differences, respectively.
*Patients registered to fulfil the ASAS criteria for axSpA and not to fulfil the modified New York criteria (nr-axSpA) or patients registered as fulfilling the modified New York criteria (r-axSpA).
ASAS, Assessment in SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; AxSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; CRP, C-reactive protein; HLA-B27, human leukocyte antigen B27; nr-axSpA, non-radiographic axSpA; Pct., percentage; r-axSpA, radiographic-axSpA; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor.

DISCUSSION

This study is the first to quantify sex differences in treatment response and retention rates from axSpA patients initiating their first TNFi among 15 European countries, including data from over 27 000 patients. We observed substantially reduced treatment effectiveness in women compared with men. At 6 months, the probability of having ASDAS-CRP CII was 19% lower in women than men. Moreover, over a 2-year study period, women had an increased risk of 71% for discontinuing TNFi treatment compared with men.

We quantified the impact of sex on treatment response in European countries and confirmed that women have a reduced probability of TNFi response compared with men.[11–19 24–26] Our real-world data represent a large part of Europe and can be generalised to clinical practice. The main findings were confirmed in half of the individual countries. In the other half, the number of participants may have been insufficient for sex comparison and the results showed a similar trend, though they were not statistically significant. The observed sex differences were present in both patients classified as r-axSpA and nr-axSpA, although the available data on the mNYc was very limited. The presence of HLA-B27, arthritis or enthesitis, or both conditions, did not affect our estimated effects. This supports our hypothesis that sex differences are prevalent regardless of the spectrum of the disease. These results are in line with other published studies,[11–19 24–26] demonstrating that the observed differences between women and men are consistent. To improve care for women with axSpA, we must better understand the pathophysiology of sex differences in treatment outcomes. Further research is needed to explore sex-tailored treatment strategies and their potential benefits. By gaining a better understanding of these differences, we can work towards more personalised treatment options for patients with axSpA.

We observed a strong relationship between the female sex and a decreased retention rate, which aligns with previous studies (HR 1.5–3.2).[11 14 19 27–29] Overall, treatment discontinuation occurred more frequently in women during the 2 years of follow-up; moreover, the separation of the survival curves transpired early and appeared to increase gradually over time. This is in contrast to the observed sex differences in treatment response, which seemed to decrease as time progressed, and reaffirms the importance of sex by illustrating that its effect on treatment is not transient but further exacerbated over time. In the stratified analyses, we noticed a remarkably high retention rate in the Dutch AmSpA registry. This may be explained by the early establishment of the registry in 1999, which was earlier than in most other countries. The first TNFi was introduced at that time, and no other biological treatments were available. Moreover, at that time, the most severe cases of r-axSpA patients were included, as opposed to later periods. Retention rates may provide a different perspective on treatment effectiveness compared with treatment response and may be less susceptible to subjective changes.

The observed sex differences in the effectiveness of a first TNFi in axSpA may be attributed to various factors, such as differences in body composition, distinct underlying molecular and cellular disease mechanisms (as suggested by variations in gene expression profiles), and differences in the manifestation and course of the disease.[4–6] Future studies are needed to determine the potential contribution of these factors to the observed differences in treatment effectiveness. Preliminary

Table 3 Sex and association with ASDAS-CRP CII at 6 months in patients with axSpA (women vs men)

			Unadjusted				Adjusted			
Country	No of patients	Pct. of women	Risk difference		Relative risk		Risk difference		Relative risk	
Switzerland	168	46	0.21	(0.067 to 0.36)	0.69	(0.51 to 0.89)	0.19	(0.049 to 0.33)	0.73	(0.55 to 0.92)
Portugal	556	48	0.20	(0.12 to 0.28)	0.70	(0.60 to 0.81)	0.19	(0.11 to 0.27)	0.71	(0.61 to 0.83)
Slovenia	99	49	0.19	(–0.009 to 0.39)	0.72	(0.48 to 1.02)	0.15	(–0.060 to 0.34)	0.78	(0.51 to 1.11)
Norway	890	38	0.11	(0.042 to 0.19)	0.79	(0.68 to 0.92)	0.10	(0.032 to 0.17)	0.81	(0.71 to 0.94)
Sweden	1014	46	0.12	(0.055 to 0.18)	0.81	(0.71 to 0.90)	0.11	(0.052 to 0.17)	0.81	(0.73 to 0.91)
Denmark	1251	41	0.097	(0.044 to 0.15)	0.83	(0.74 to 0.92)	0.097	(0.041 to 0.15)	0.83	(0.74 to 0.92)
Turkey	663	42	0.10	(0.027 to 0.17)	0.86	(0.77 to 0.96)	0.094	(0.022 to 0.16)	0.87	(0.78 to 0.97)
Netherlands	145	32	0.076	(–0.088 to 0.24)	0.85	(0.53 to 1.22)	0.075	(–0.11 to 0.25)	0.85	(0.52 to 1.26)
UK	184	32	0.049	(–0.10 to 0.20)	0.90	(0.58 to 1.26)	0.059	(–0.094 to 0.21)	0.88	(0.56 to 1.25)
Romania	188	30	0.058	(–0.015 to 0.15)	0.94	(0.85 to 1.02)	0.062	(–0.017 to 0.15)	0.94	(0.84 to 1.02)
Czech Republic	1125	28	0.046	(–0.006 to 0.098)	0.95	(0.89 to 1.01)	0.037	(–0.012 to 0.085)	0.96	(0.90 to 1.01)
Iceland	25	36	0.11	(0.000 to 0.36)	0.89	(0.64 to 1.00)	0.028	(–0.22 to 0.23)	0.98	(0.77 to 1.32)
Finland	143	39	0.012	(–0.19 to 0.15)	1.03	(0.73 to 1.42)	0.031	(–0.21 to 0.14)	1.07	(0.77 to 1.44)
Pooled	6451	39	0.13	(0.10 to 0.15)	0.81	(0.77 to 0.84)	0.097	(0.074 to 0.12)	0.85	(0.82 to 0.88)

Countries are ordered from most significant unadjusted relative risk to least significant relative risk. The adjusted models in the logistic regression analysis included age and TNFi start year for the separate countries. Absolute risk difference and relative risk with 95% CIs are provided.
ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with C-reactive protein; axSpA, axial spondyloarthritis; CII, clinically important improvement; Pct., percentage.

Table 4 Sex and association with secondary outcomes in patients with axSpA (women vs men)

	6 months				12 months				24 months			
	Total (N)	Unadjusted relative risk		Adjusted relative risk		Total (N)	Unadjusted relative risk		Adjusted relative risk		Total (N)	Unadjusted relative risk		Adjusted relative risk	
ASDAS-CRP CII	6451	0.81	(0.77 to 0.84)*	0.85	(0.82 to 0.88)*	4386	0.82	(0.78 to 0.86)*	0.88	(0.84 to 0.91)*	3092	0.86	(0.81 to 0.90)*	0.89	(0.85 to 0.94)*
ASDAS-CRP MI	6451	0.69	(0.63 to 0.74)*	0.76	(0.71 to 0.82)*	4386	0.74	(0.67 to 0.80)*	0.83	(0.77 to 0.89)*	3092	0.79	(0.72 to 0.87)*	0.87	(0.79 to 0.95)
ASDAS-CRP ID	9840	0.66	(0.61 to 0.71)*	0.66	(0.61 to 0.70)*	6822	0.71	(0.65 to 0.76)*	0.73	(0.67 to 0.78)*	5053	0.73	(0.66 to 0.79)*	0.76	(0.69 to 0.82)*
ASDAS-CRP LDA	9840	0.80	(0.77 to 0.83)*	0.81	(0.78 to 0.84)*	6822	0.81	(0.77 to 0.84)*	0.83	(0.80 to 0.87)*	5053	0.83	(0.79 to 0.87)*	0.86	(0.82 to 0.89)*
ASAS20	7435	0.82	(0.77 to 0.87)*	0.89	(0.84 to 0.93)*	4966	0.82	(0.77 to 0.87)*	0.92	(0.87 to 0.96)	3243	0.83	(0.77 to 0.89)*	0.92	(0.87 to 0.98)
ASAS40	8754	0.82	(0.76 to 0.88)*	0.90	(0.84 to 0.96)	5829	0.78	(0.71 to 0.84)*	0.90	(0.84 to 0.97)	3765	0.81	(0.74 to 0.89)*	0.94	(0.86 to 1.02)
BASDAI remission	13 045	0.71	(0.68 to 0.74)*	0.73	(0.69 to 0.76)*	9533	0.76	(0.72 to 0.80)*	0.78	(0.75 to 0.82)*	7137	0.76	(0.72 to 0.80)*	0.78	(0.74 to 0.82)*
BASDAI LDA	13 045	0.80	(0.79 to 0.83)*	0.83	(0.81 to 0.85)*	9533	0.82	(0.80 to 0.85)*	0.85	(0.83 to 0.87)*	7137	0.84	(0.82 to 0.87)*	0.86	(0.84 to 0.89)*
BASDAI50	9574	0.79	(0.76 to 0.83)*	0.83	(0.80 to 0.86)*	6938	0.82	(0.78 to 0.86)*	0.86	(0.82 to 0.90)*	5056	0.84	(0.80 to 0.88)*	0.87	(0.83 to 0.91)*

Logistic regression analysis of secondary outcomes. Absolute relative risks with 95% CIs are provided.
The adjusted models included country, age and TNFi start year.
*Statistically significant with p<0.000926 (Bonferroni correction).
ASAS20, 40, Assessment of SpondyloArthritis international Society 20%, 40% response criteria; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with C-reactive protein; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CII, clinically important improvement; ID, inactive disease; LDA, low disease activity; MI, major improvement.

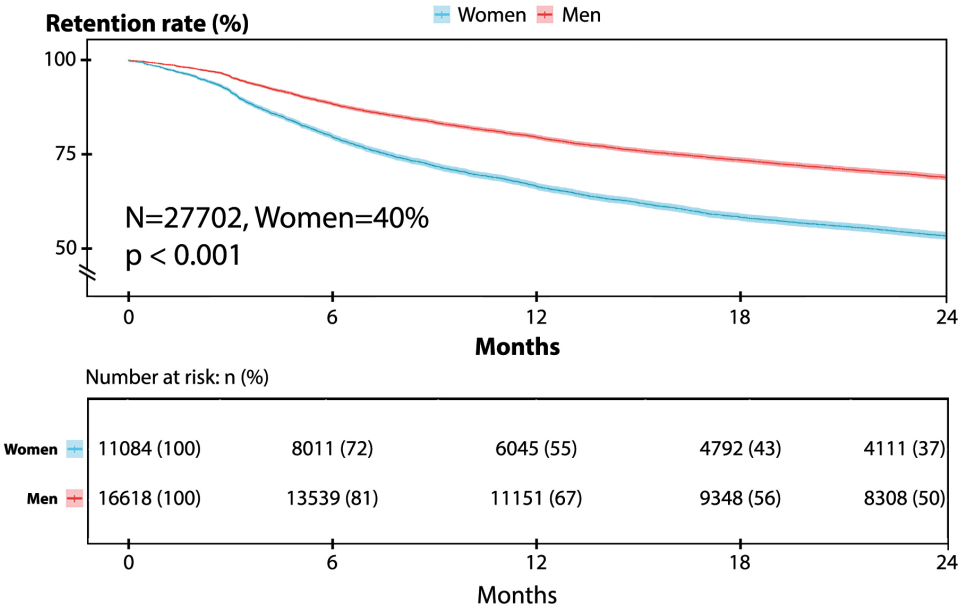

Figure 2 Sex differences in 24-month retention rates in first-line tumour necrosis factor inhibitors in axial spondyloarthritis patients in EuroSpA (Kaplan-Meier, log-rank test). The number of patients and the percentage of women are provided. EuroSpA, European spondyloarthritis.

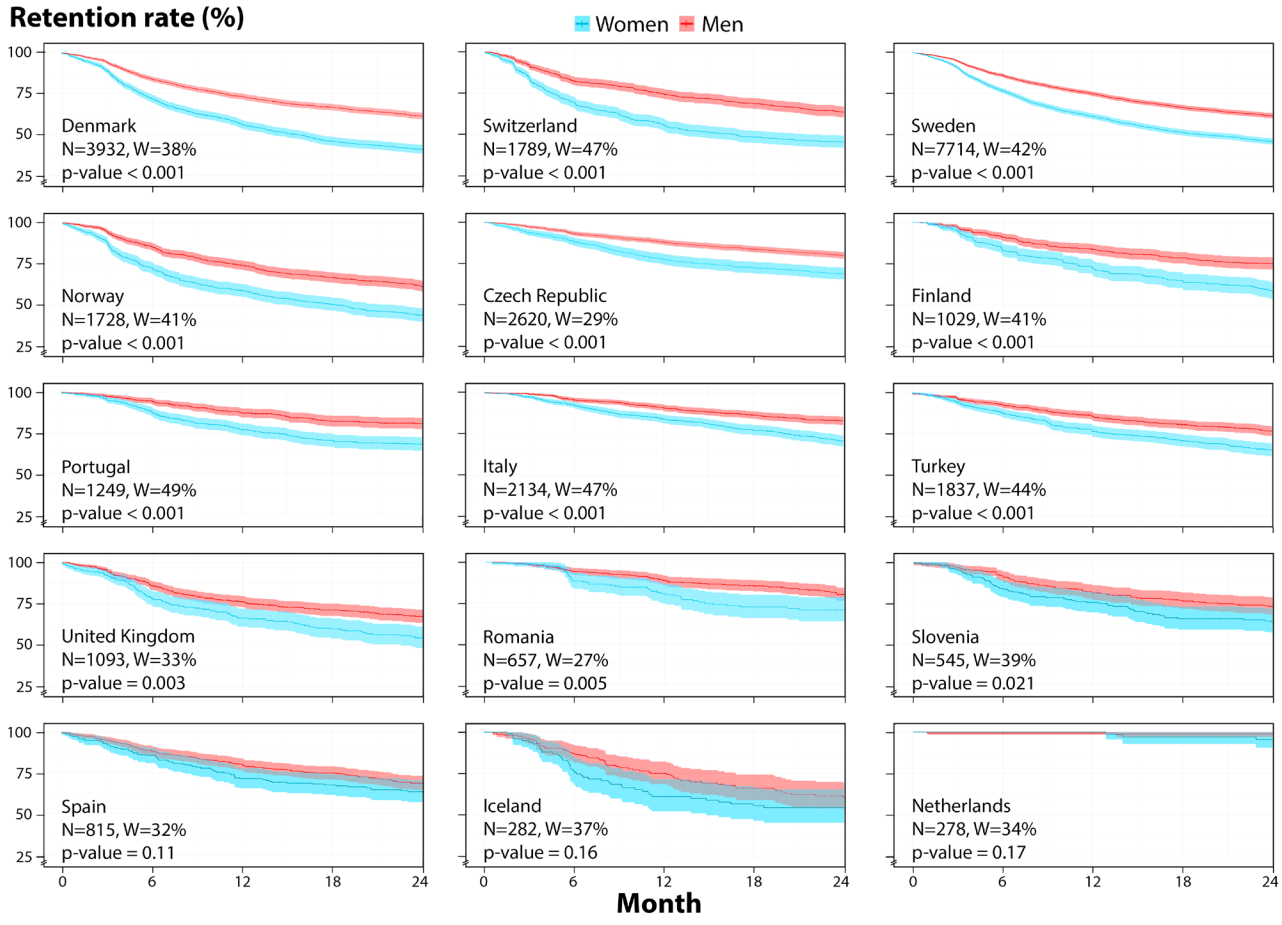

Figure 3 Sex differences in 24-month retention rates in first-line tumour necrosis factor inhibitors in axial spondyloarthritis patients, stratified per country (Kaplan-Meier, log-rank test). Countries are ranked from most significant to least significant. The number of patients and the percentage of women are provided.

results from another study suggest that higher body fat percentage in women may reduce the effectiveness of TNFi, possibly due to increased production of proinflammatory cytokines in fat tissue.[10] In addition, sex differences in the absorption, metabolism and excretion of pharmacological agents have been described,[8] which may result in higher TNFi concentrations in women and potentially increased adverse events,[17 30] leading to reduced treatment retention. Another unexplored area of research is the role of gender identity in treatment response. Gender identity, as defined by Mauvais-Jarvis *et al*, describes the fluidity of how a person perceives oneself as a woman or a man, which affects feelings and behaviours.[31] This could influence patient-reported outcome measures. Moreover, gender identity could interact with biological sex. Future studies are needed to explore the interplay of biological sex and gender identity on treatment response in axSpA.

It is possible that differences in the level of inflammation due to high disease activity, present at the time treatment is initiated, contribute to the sex differences observed in axSpA. On average, men tend to have more objective signs of inflammation, such as elevated CRP levels and visible inflammation on imaging, which are associated with a higher probability of response to TNFi.[4–6] In addition, it has been demonstrated that sex could influence phenotypic aspects in axSpA, determining the main involvement of the spine with damage and less frequently bilateral sacroliliitis.[32] Women are also more frequently diagnosed with nr-axSpA, possibly due to radiographic changes being more prevalent in men.[4 5] Compared with r-axSpA, the probability of a good response to TNFi may be lower in nr-axSpA, especially in the absence of objective inflammation, or when the r-axSpA is severe.[33 34] The diagnosis of nr-axSpA in the absence of positive imaging findings relies on clinical criteria, which can be considered less definitive than imaging. A study in the DESIR cohort revealed that women were more likely to be classified as axSpA using the clinical arm of the ASAS classification system.[35] Although these criteria are not intended for diagnosis, this suggests that women may be more likely to be overdiagnosed in the absence of objective signs of inflammation. Women might also have more often false positive MRI findings from recent pregnancy (<1 year),[36] although this group is small. In cases where the diagnosis is inaccurate and the complaints are not indicative of active axSpA, the treatment is not expected to be effective.

However, these factors do not fully account for the sex differences observed in patients with r-axSpA. Most of the previous literature was conducted in patients with r-axSpA,[11 13 14 16 17 19 25 27–29] and our subgroup analyses have revealed sex differences in CII in both patients classified as nr-axSpA and r-axSpA, suggesting that other factors may be contributing to the observed treatment disparities. Further research is needed to identify these factors and determine how they can be addressed in the diagnosis and treatment of axSpA. By gaining a better understanding of these differences, we can improve the care and outcomes for patients with this condition, particularly women.

This study has several strengths, including the inclusion of a large number of axSpA patients and extensive secondary, sensitivity and subgroup analyses that support our conclusions. However, our study also has three limitations that should be addressed.

First, compared with the total number of patients with available data on retention rates, the percentage of missing data in treatment response is high.

This raises the possibility of selection bias due to missingness. Nevertheless, the baseline characteristics of the population with retention rates and available ASDAS-CRP measurements were comparable, supporting the assumption that the data were missing completely at random. If the data were missing completely at random, then the results are expected to be unbiased.[37] Lastly, the examination of multiple secondary cohorts, defined by the availability of secondary outcomes, consistently revealed sex differences, reducing the likelihood that the sex differences observed in the primary cohort were a result of selection bias.

Moreover, we cannot exclude the possibility that selection bias has occurred due to the loss of follow-up. For example, the effect sizes for treatment response decreased as time progressed, possibly due to women with the worst outcome dropping out of the analyses (eg, switching to another treatment). This implies that the estimated effects are probably underestimating the actual effect size. However, we selected 6 months as our primary endpoint to mitigate this potential bias.

Second, due to a high percentage of missing data in mNY and ASAS classification criteria, we could only perform subgroup analyses in r-axSpA and nr-axSpA patients in a relatively small sample. Therefore, the precision of the estimated effects in these analyses is low, and their interpretation warrants caution.

Third, while the primary objective of this study was to explore the total effect of sex on treatment response, it would have been valuable to examine whether specific factors, such as disease duration, CRP levels, radiographic evidence of sacroillitis on imaging, (extra)musculoskeletal manifestations, and comorbidities such as history of malignancy, fibromyalgia and depression, could account for the observed sex differences in treatment response. Nevertheless, since sex is predetermined at birth, these factors can be classified as mediators rather than confounders. Consequently, the lack of adjustment for these factors should not introduce bias to our estimated effects. To gain a more comprehensive understanding of this subject, future studies should focus on examining the influence of these factors on sex differences in treatment responses and retention rates.

In conclusion, this multinational observational cohort study in axSpA patients treated with their first TNFi demonstrated reduced treatment response and substantially lower retention rates in women compared with men.

To improve care for both men and women with axSpA, but particularly women, we must better understand sex differences in treatment outcomes in clinical practice and research.

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