Response to Tumor Necrosis Factor Inhibition in Male and Female Patients with Ankylosing Spondylitis: Data from a Swiss Cohort

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ABSTRACT. ***Objective.*** To investigate sex differences in connection with the effectiveness of tumor necrosis factor inhibitors (TNFi) in patients with ankylosing spondylitis (AS).

Methods. A total of 440 patients with AS (294 men; 146 women) initiating a first TNFi in the prospective Swiss Clinical Quality Management Cohort were included. We evaluated the proportion of patients achieving the 20% and 40% improvement in the Assessment of Spondyloarthritis international Society criteria (ASAS20 and ASAS40) as well as Ankylosing Spondylitis Disease Activity Score (ASDAS) improvement and status scores at 1 year. Patients having discontinued TNFi were considered nonresponders. Logistic regression analyses were performed to adjust for important predictors of response.

Results. Compared to men, female patients had lower mean C-reactive protein levels, better spinal mobility, and more peripheral disease at the start. There was no sex disparity with regard to the ASDAS, the Bath Ankylosing Spondylitis Disease Activity and Functional indices, and the quality of life. At 1 year, 52% of women and 63% of men achieved an ASAS20 response (OR 0.63, 95% CI 0.37–1.07, p = 0.09). An inactive disease status (ASDAS < 1.3) was reached by 18% of women and 26% of men (OR 0.65, 95% CI 0.32–1.27, p = 0.22). These sex differences in response to TNFi were more pronounced in adjusted analyses (OR 0.34, 95% CI 0.16–0.71, p = 0.005 for ASAS20 and OR 0.10, 95% CI 0.03–0.31, p < 0.001 for ASDAS < 1.3) and confirmed for all the other outcomes assessed.

Conclusion. In AS, fewer women respond to TNFi and women show a reduced response in comparison to men. (J Rheumatol First Release February 15 2018; doi:10.3899/jrheum.170166)

Key Indexing Terms:
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While ankylosing spondylitis (AS) has traditionally been considered a disease with male predominance[1], various investigations have demonstrated a more equitable sex ratio in the nonradiographic form of axial spondyloarthritis (axSpA)[2,3,4]. Differences in AS disease phenotype that have been demonstrated between men and women include more severe spinal radiographic changes in men, while female patients present with more peripheral arthritis, self-reported disease activity, and functional impairment, as well as a lower quality of life[5,6]. Moreover, markers of inflammation [elevation of C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) inflammation of the spine] are more frequently associated with the male sex[7,8]. There remains a substantially longer diagnostic delay for women, probably because the disease is still perceived as predominantly a male condition, and because of the later onset of the disease in women[9]. It remains unknown whether all these factors translate into the lower effectiveness of tumor necrosis factor inhibitors (TNFi) observed in female patients with AS in several studies. Male sex was associated with a better TNFi drug survival in several observational studies[10,11,12] and was also identified as a predictor of better response in some cohort studies, but not in others[10,11,12,13,14]. The latter inconsistency may be related to the different outcome variables assessed and to disparities in baseline characteristics across the sexes in these studies.

The following factors have been found to be important predictors of response: age, physical function as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI), enthesitis, elevated baseline CRP, and HLA-B27 genotype. They also enable adequate prediction of outcome upon treatment with TNFi in various subpopulations[15]. Smoking was associated with impaired response to TNFi in other studies[16,17]. An inverse relationship between increase in body mass index (BMI) and TNFi response has also been demonstrated[14]. In addition to results of observational studies, women have also been shown to have less improvement in AS outcome measures in a posthoc analysis of pooled randomized controlled trials of etanercept (ETN)[18]. In the latter study, female patients had a more severe burden of disease at baseline.

The aim of our study was to investigate potential sex differences with regard to the effectiveness of TNFi in patients with AS after adjustment for important predictors of response in a large prospective observational cohort.

MATERIALS AND METHODS

Study population. This study is a longitudinal analysis of the ongoing Swiss Clinical Quality Management (SCQM) cohort of patients with a diagnosis of axSpA recruited from January 2005 to April 2016, as previously described[4]. Assessments at baseline and annual visits were performed according to the recommendations of Assessment of Spondyloarthritis international Society (ASAS)[19]. Patients were included in the current study if they fulfilled the ASAS criteria for axSpA, additionally presented with definite radiographic sacroiliitis according to the modified New York criteria[20] for AS, with pelvic radiographs scored centrally[4], and if baseline disease activity information at initiation of a first TNFi was available. Patients with concurrent fibromyalgia (FM) at any visit (as indicated by the treating rheumatologist in the comorbidity questionnaire) were excluded (n = 9). The rheumatologist is automatically led through the comorbidity questionnaire at the time of reporting the results of the clinical examination in the online database. Standard instruments to assess FM or the fulfillment of classification criteria for FM were, however, not required. The study was approved by the Ethics Commission of the Canton of Zurich (KEK-ZH-Nr. 2014-0439). Written informed consent was obtained from all patients.

Response to anti-TNF treatment. Treatment response to the first TNFi was assessed in patients with an available outcome at 1 year (± 6 mos). In the case of TNFi discontinuation before the first outcome assessment, patients were considered nonresponders (response/tolerance analysis)[21]. The large window of response assessment was mandated by the structure of SCQM because annual followup visits recommended after inclusion did not necessarily match yearly intervals after initiation of treatment. Alternatively, response was measured in patients still treated with the first TNFi at 1 year (completer analysis). The primary outcome was achievement of the 20% improvement ASAS criteria (ASAS20)[19]. The following additional efficacy variables were assessed: ASAS40 response criteria, the proportion of patients achieving an Ankylosing Spondylitis Disease Activity Score (ASDAS) < 2.1 (reflecting moderate disease activity) or ASDAS < 1.3 (corresponding to inactive disease), as well as a clinically important improvement in ASDAS (change of ≥ 1.1 between baseline and followup) or a major improvement in ASDAS (change of ≥ 2.0)[19,22]. ASDAS is calculated using CRP levels, after assuming a fixed value of 2 for CRP levels < 2 mg/l, as previously proposed[23]. A further secondary outcome was treatment maintenance, estimated as the time individual patients maintained their first TNFi treatment, using start and stop dates indicated by the treating rheumatologist. Observations were censored at the last visit registered in SCQM.

Statistical analysis. We compared baseline characteristics between women and men using the Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. The significance of differences in response rates between women and men at 1 year was assessed using the Fisher's exact test. Logistic regression analysis was used to estimate an adjusted ratio for ASAS20, ASAS40, ASDAS clinically important or major improvement, ASDAS status score < 2.1 and < 1.3. The effect of sex on the response to treatment is unlikely to be confounded by other predictors for good response, because sex is not affected by these predictors. However, other predictors for good response may be mediators of the effect of sex on treatment response. The following variables were included in a first model: age, BASFI, enthesitis, elevated CRP status, and HLA-B27. Smoking, disease duration, BASMI and peripheral arthritis, type of anti-TNF agent (monoclonal antibodies vs ETN), as well as presence of overweight (BMI 25 to 30) and obesity (BMI > 30) versus normal weight were added as covariables in an additional model. We tested for interactions between sex and the other variables. Drug maintenance was described with Kaplan-Meier plots. We used the log-rank test to test for differences between men and women. R statistical software (R Development Core Team, 2011) was used for all analyses. All tests were 2-sided, with a significance level set at 0.05.

RESULTS

Baseline assessments. A total of 440 patients with AS starting a first TNFi after inclusion in SCQM fulfilled the inclusion

criteria (294 men and 146 women). Their baseline characteristics are shown in Table 1. Women presented with a trend for a shorter disease duration and a longer diagnostic delay, as well as a lower proportion of HLA-B27 positivity in comparison to men, confirming results found in a preliminary analysis in the whole SCQM cohort[9]. Women had a lower BMI than men and were more likely to have peripheral disease (arthritis and enthesitis). In contrast, axial mobility, as assessed by the BASMI, was more severely impaired and CRP levels were higher in men. Differences were small and not statistically significant between men and women regarding the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and ASDAS levels, the amount of self-reported functional limitation (BASFI), the impairment in health-related quality of life (EQ-5D), and the values for patient's global assessment (PtGA) and physician's global assessment (PGA).

Treatment response. A followup visit at 1 year ± 6 months was available for response analyses in 340/440 patients with AS (77%). Baseline characteristics of this population, stratified by sex, are shown in Table 2. In patients with available outcome, TNFi was stopped in 25 female and 44 male patients before outcome assessment. We found a similar distribution of the reasons for TNFi discontinuation by sex: ineffectiveness 52% versus 57%, adverse events 28% versus 25%, remission 0% versus 4%, and other reasons 20% versus 14%, for women and men, respectively (overall p = 0.77).

Crude response rates are shown in Table 3. The proportion of patients reaching an ASAS20 response was numerically lower in women versus men: 52% versus 63%, OR 0.63, 95% CI 0.37–1.07, p = 0.09. Lower response rates were also found in women versus men for the additional outcomes assessed, although the results did not reach statistical significance (Table 3).

Table 1. Baseline characteristics in women versus men with AS at start of first TNFi. Except where indicated otherwise, values are mean (SD).

Variable	Total, n = 440	Women, n = 146	Men, n = 294	p
Age, years	440	40.5 (11.5)	40.4 (11.8)	0.90
Age at onset, yrs	**436**	**27.3 (8.8)**	**25.0 (7.8)**	**0.03**
Symptom duration, yrs	436	13.2 (10.1)	15.3 (11.4)	0.09
Diagnostic delay, yrs	436	6.4 (6.6)	5.1 (6.1)	0.07
HLA-B27–positive, %	**393**	**71.5**	**84.8**	**0.003**
BASDAI	403	5.8 (2.0)	5.5 (1.9)	0.11
PtGA	407	6.3 (2.4)	6.6 (2.3)	0.25
PGA	423	4.9 (1.9)	5.0 (1.8)	0.69
ASDAS	382	3.4 (1.0)	3.6 (0.9)	0.07
CRP, mg/l, median (IQR)	**415**	**8.0 (3.5–14.0)**	**10.0 (5.0–23.0)**	**0.003**
Elevated CRP, %	412	53.4	62.7	0.09
BASFI	409	4.4 (2.5)	4.3 (2.5)	0.69
BASMI	**389**	**1.9 (1.7)**	**3.0 (2.3)**	**< 0.001**
EQ-5D	402	54.9 (21.4)	54.5 (22.0)	0.98
Current peripheral arthritis, %	**430**	**43.1**	**30.8**	**0.01**
No. swollen joints	**423**	**1.3 (3.7)**	**0.6 (1.7)**	**0.01**
Current enthesitis, %	**432**	**75.2**	**64.5**	**0.03**
Modified MASES	**430**	**3.1 (3.6)**	**2.2 (2.9)**	**0.02**
Dactylitis ever, %	438	9.7	10.2	1.00
Uveitis ever, %	383	28.2	25.9	0.62
Taking sulfasalazine, %	440	5.5	6.5	0.83
Taking methotrexate, %	440	5.5	6.5	0.83
Taking NSAID, %	404	96.4	95.1	0.62
Current smokers, %	**393**	**35.1**	**47.3**	**0.02**
BMI	**389**	**24.6 (4.7)**	**25.9 (4.0)**	**< 0.001**
First TNFi used, %	440			0.67
Adalimumab		30.8	33.0	
Certolizumab		0.7	0.3	
Etanercept		28.8	29.6	
Golimumab		17.1	12.6	
Infliximab		22.6	24.5	

Data in bold face are statistically significant. AS: ankylosing spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score (modification refers to the inclusion of the plantar fascia in the count); NSAID: nonsteroidal antiinflammatory drugs; TNFi: tumor necrosis factor inhibitor; PtGA: patient's global assessment; PGA: physician's global assessment; IQR: interquartile range; BMI: body mass index.

Table 2. Baseline characteristics of patients with AS starting a first course of TNFi for different outcome analyses. Except where indicated otherwise, values are the mean (SD).

	A. Response/Tolerance Analysis*				B. Completer Analysis**				C. Drug Retention Analysis			
Variable	Total, n = 340	Women, n = 102	Men, n = 238	p	Total, n = 275	Women, n = 77	Men, n = 198	p	Total, n = 406	Women, n = 130	Men, n = 276	p
Age, years	340	40.0 (11.2)	40.0 (11.7)	0.91	275	40.1 (10.9)	39.3 (11.5)	0.58	406	40.0 (11.2)	40.2 (11.8)	0.96
Age at onset, yrs	338	26.5 (8.2)	24.8 (7.8)	0.12	273	25.9 (8.0)	24.6 (7.8)	0.30	403	26.4 (8.3)	25.0 (7.8)	0.19
Symptom duration, yrs	338	13.4 (9.4)	15.3 (11.0)	0.30	273	14.1 (9.4)	14.7 (10.5)	0.98	403	13.6 (9.6)	15.3 (11.2)	0.30
Diagnostic delay, yrs	338	6.5 (6.2)	5.3 (6.2)	0.09	**273**	**6.9 (6.3)**	**5.1 (6.2)**	**0.03**	**403**	**6.7 (6.6)**	**5.2 (6.1)**	**0.03**
HLA-B27–positive, %	**303**	**72.7**	**86.5**	**0.007**	249	79.1	86.3	0.17	**362**	**71.9**	**84.7**	**0.006**
BASDAI	316	5.7 (2.0)	5.5 (2.0)	0.29	257	5.7 (2.0)	5.4 (2.0)	0.23	374	5.7 (2.0)	5.5 (1.9)	0.29
BASDAI ≥ 4	316	78.3	77.2	0.88	257	79.5	76.1	0.62	374	79.2	76.4	0.60
PGA	328	5.0 (1.8)	5.0 (1.8)	0.75	266	5.0 (1.8)	4.9 (1.8)	0.82	390	4.9 (1.8)	5.0 (1.8)	0.49
PtGA	319	6.2 (2.5)	6.6 (2.4)	0.14	260	6.2 (2.5)	6.6 (2.4)	0.19	377	6.2 (2.5)	6.2 (2.3)	0.09
ASDAS	300	3.5 (1.1)	3.6 (0.9)	0.10	246	3.5 (1.1)	3.6 (0.9)	0.30	**355**	**3.4 (1.0)**	**3.6 (0.9)**	**0.05**
ASDAS ≥ 2.1	300	88.6	93.5	0.15	246	88.1	93.3	0.19	355	89.0	93.9	0.13
CRP, mg/l, median (IQR)	321	8 (4.3–16)	11 (5–25.5)	0.09	261	8.4 (5–19)	11.0 (5–26)	0.25	**384**	**8.0 (4–14)**	**10.0 (5–24)**	**0.01**
Elevated CRP, %	318	58.7	64.2	0.37	258	62.3	66.1	0.66	381	55.1	63.5	0.14
BASFI	321	4.3 (2.6)	4.4 (2.4)	0.79	261	4.3 (2.6)	4.3 (2.5)	0.98	379	4.3 (2.6)	4.3 (2.4)	0.90
BASMI	**297**	**1.9 (1.7)**	**3.0 (2.3)**	**< 0.001**	**239**	**2.1 (1.7)**	**2.9 (2.4)**	**0.02**	**357**	**1.9 (1.7)**	**3.0 (2.3)**	**< 0.001**
EQ-5D	316	55.1 (21.2)	53.9 (22.0)	0.89	257	56.8 (20.8)	55.2 (21.6)	0.81	373	55.7 (21.5)	54.0 (22.1)	0.53
Current periph. arthritis,%	**330**	**43.0**	**29.1**	**0.02**	**270**	**43.4**	**29.4**	**0.03**	**396**	**42.2**	**29.9**	**0.02**
No. swollen joints	**324**	**1.4 (4.0)**	**0.6 (1.8)**	**0.01**	**266**	**1.2 (3.1)**	**0.7 (1.9)**	**0.04**	**389**	**1.2 (3.6)**	**0.6 (1.7)**	**0.03**
Current enthesitis, %	**332**	**77.2**	**65.4**	**0.04**	**269**	**79.0**	**64.2**	**0.02**	**398**	**78.3**	**64.7**	**0.008**
Modified MASES	**330**	**3.0 (3.5)**	**2.2 (2.8)**	**0.04**	**267**	**2.9 (2.7)**	**2.1 (2.7)**	**0.04**	**396**	**3.1 (3.6)**	**2.2 (2.8)**	**0.02**
Dactylitis ever, %	338	9.9	8.9	0.84	274	11.7	7.1	0.23	404	9.3	8.4	0.85
Uveitis ever, %	300	29.6	25.5	0.48	240	33.9	26.9	0.34	361	29.8	25.1	0.37
Taking sulfasalazine, %	340	7.8	6.7	0.82	275	9.1	7.6	0.63	406	6.2	6.2	1.00
Taking methotrexate, %	340	5.9	5.5	1.00	275	7.8	5.6	0.58	406	4.6	5.8	0.81
Taking NSAID, %	310	95.9	95.3	1.00	252	97.2	94.4	0.52	373	96.8	95.2	0.59
Current smoking, %	**306**	**34.0**	**47.6**	**0.03**	248	34.7	47.2	0.09	**363**	**34.5**	**47.8**	**0.02**
BMI	**299**	**23.8 (4.3)**	**25.9 (3.9)**	**< 0.001**	**243**	**23.6 (4.1)**	**25.8 (3.9)**	**< 0.001**	**358**	**24.2 (4.6)**	**25.9 (3.9)**	**< 0.001**

Data in bold face are statistically significant. *Response in patients with available outcome at 1 year, patients having discontinued the first TNFi in the meantime being considered nonresponders. **Analysis in patients still treated with the first TNFi at 1 year. A. Patients starting a first TNFi with available baseline and followup visit at 1 year. B. Patients still treated with the first TNFi at 1 year. C. Patients starting a first TNFi with available start and stop dates of drug application. AS: ankylosing spondylitis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using CRP; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score (modification refers to the inclusion of the plantar fascia in the count); NSAID: nonsteroidal antiinflammatory drugs; TNFi: tumor necrosis factor inhibitor; PtGA: patient's global assessment; PGA: physician's global assessment; IQR: interquartile range; BMI: body mass index.

Table 3. Clinical outcome of women versus men after 1 year of treatment with a first TNF inhibitor (Response/Tolerance Analysis[#]).

	Unadjusted Analyses						Adjusted Model 1*				Adjusted Model 2**			
Outcome	N	Women, %	Men, %	OR	95% CI	p	N	OR	95% CI	p	N	OR	95% CI	p
ASAS20	293	52	63	0.63	0.37–1.07	0.09	244	0.48	0.27–0.87	0.02	210	0.34	0.16–0.71	0.005
ASAS40	293	40	46	0.79	0.46–1.35	0.37	244	0.60	0.33–1.09	0.10	210	0.44	0.21–0.91	0.03
ASDAS improvement ≥ 1.1	262	51	61	0.69	0.38–1.22	0.21	228	0.52	0.26–1.05	0.07	196	0.27	0.10–0.67	0.006
ASDAS < 2.1	284	48	53	0.82	0.48–1.42	0.51	230	0.47	0.24–0.91	0.03	198	0.26	0.11–0.59	0.002
ASDAS improvement ≥ 2	262	23	32	0.62	0.31–1.19	0.14	228	0.48	0.22–0.99	0.05	196	0.26	0.09–0.67	0.007
ASDAS < 1.3	284	18	26	0.65	0.32–1.27	0.22	230	0.29	0.11–0.68	0.007	198	0.10	0.03–0.31	< 0.001

[#]Response in patients with available outcome at 1 year, patients having discontinued the first TNF inhibitor in the meantime being considered nonresponders. *Model 1: adjustment for age, HLA-B27, BASFI, elevated CRP status, enthesitis. **Model 2: additional adjustment for disease duration, BASMI, peripheral arthritis, current smoking, type of anti-TNF agent, as well as BMI categories. ASAS20 and ASAS40 = 20% and 40% improvement, respectively, according to the Assessment in Spondyloarthritis international Society criteria. ASDAS: Ankylosing Spondylitis Disease Activity Score; TNF: tumor necrosis factor; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; BMI: body mass index.

Adjusted response analyses were performed in patients with available covariate data (model 1 and 2 in Table 3). To better define this latter subset of patients, we performed crude response analyses and found similar outcomes compared to the whole population (data not shown). In comparison to men, responses to TNFi in women were significantly lower after adjustment for important predictors of response: OR 0.48, 95% CI 0.27–0.87, p = 0.02 and OR 0.34, 95% CI 0.16–0.71, p = 0.005 for the ASAS20 responses in model 1 and 2, respectively (Table 3). Treatment response in women was also found to be diminished in comparison to men in the adjusted analyses of the other outcomes measured. Sex disparities regarding response to anti-TNF agents were also observed in multiple adjusted analyses of patients still treated with the first TNFi (completer analyses), though to a lesser extent (Table 4).

Drug retention. Data on start and stop dates for a first TNFi were available in 406 patients. Baseline characteristics of these patients are shown in Table 2. Median TNFi maintenance was 5.2 years (95% CI 3.7–7.2) in men and 2.9 years (95% CI 2.0–5.3) in women (log-rank test p = 0.005; Figure 1).

DISCUSSION

Our observational study demonstrates that rheumatologists in real-life conditions initiate treatment with TNFi at the same level of disease burden in women and in men, because no baseline disparities across the sexes could be detected for BASDAI, BASFI, PtGA, and PGA, as well as for health-related quality of life. Distinct features mainly contributed to the burden of disease in male and female patients. We confirmed differences in disease expression: men had more severely impaired spinal mobility and higher CRP levels, while a higher proportion of women presented with peripheral disease (arthritis and enthesitis). Differences between the sexes were also found in additional predictors of good response to treatment: a higher proportion of women had nonsmoking status as well as a lower BMI, and there was a trend for shorter disease duration at initiation of anti-TNF treatment in women, though at the expense of a longer diagnostic delay.

These differences between the sexes in factors predicting the outcome of AS therapy apparently counterbalanced each other in crude response analyses to TNFi. However, women consistently presented with a significantly impaired response to anti-TNF agents at 1 year in multiple adjusted response analyses. The same values are attributed to men and women for all covariables in adjusted analyses, which might render them less representative of the whole population of men and of women with AS, respectively.

The sex difference in clinical response to TNFi cannot only be explained by the significantly shorter drug retention found in women, because the findings were confirmed in completer response analyses at 1 year. Based on recent data, an uncoupling between clinical symptoms and MRI inflammation has been suggested for female patients[8]. While in men, clinical signs and symptoms were directly associated with MRI positivity and with subsequent structural damage, symptoms attributed to axSpA occurred independently of MRI inflammation in women. The uncoupling between symptoms and inflammation in women might also explain the limited response to TNF-blocking agents in female patients. This issue could not be further investigated here, because in contrast to radiographs, MRI are not routinely collected in SCQM. Further, regarding the AS population, there is no need to perform an MRI of the sacroiliac joint for diagnostic purposes in the presence of definite radiographic sacroiliac changes in a real-life setting. A further limitation of our study was that followup visits at 1 year were available in only 77% of the patients, a finding inherent to the observational character of the SCQM cohort. However, patients with and without followup data were comparable regarding important baseline characteristics. Lower patient numbers were available for adjusted analyses. Comparable crude response rates in the whole population and in the subset of

Table 4. Clinical outcome of women versus men after 1 year of treatment with a first TNF inhibitor (Completer Analysis[#]).

	Unadjusted Analyses						Adjusted Model 1*				Adjusted Model 2**			
Outcome	N	Women, %	Men, %	OR	95% CI	p	N	OR	95% CI	p	N	OR	95% CI	p
ASAS20	240	71	75	0.81	0.41–1.63	0.51	204	0.53	0.26–1.08	0.08	175	0.31	0.12–0.80	0.02
ASAS40	240	55	55	1.02	0.55–1.89	1.00	204	0.68	0.35–1.30	0.24	175	0.45	0.20–1.02	0.06
ASDAS improvement ≥ 1.1	219	68	72	0.86	0.43–1.77	0.74	193	0.58	0.25–1.36	0.21	167	0.21	0.06–0.67	0.01
ASDAS < 2.1	232	65	63	1.07	0.56–2.07	0.88	193	0.56	0.26–1.17	0.12	167	0.27	0.10–0.68	0.007
ASDAS improvement ≥ 2	219	30	38	0.69	0.33–1.37	0.27	193	0.51	0.23–1.10	0.09	167	0.27	0.09–0.70	0.01
ASDAS < 1.3	232	24	31	0.71	0.34–1.42	0.33	193	0.33	0.13–0.80	0.02	167	0.11	0.03–0.36	< 0.001

[#]Analysis in patients still treated with the first TNF inhibitor at 1 year. ASAS20 and ASAS40 = 20% and 40% improvement, respectively, according to the Assessment in Spondyloarthritis international Society criteria. *Model 1: adjustment for age, HLA-B27, BASFI, elevated CRP status, enthesitis. **Model 2: additional adjustment for disease duration, BASMI, peripheral arthritis, current smoking, type of anti-TNF agent, as well as BMI categories. ASDAS: Ankylosing Spondylitis Disease Activity Score; TNF: tumor necrosis factor; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; BMI: body mass index.

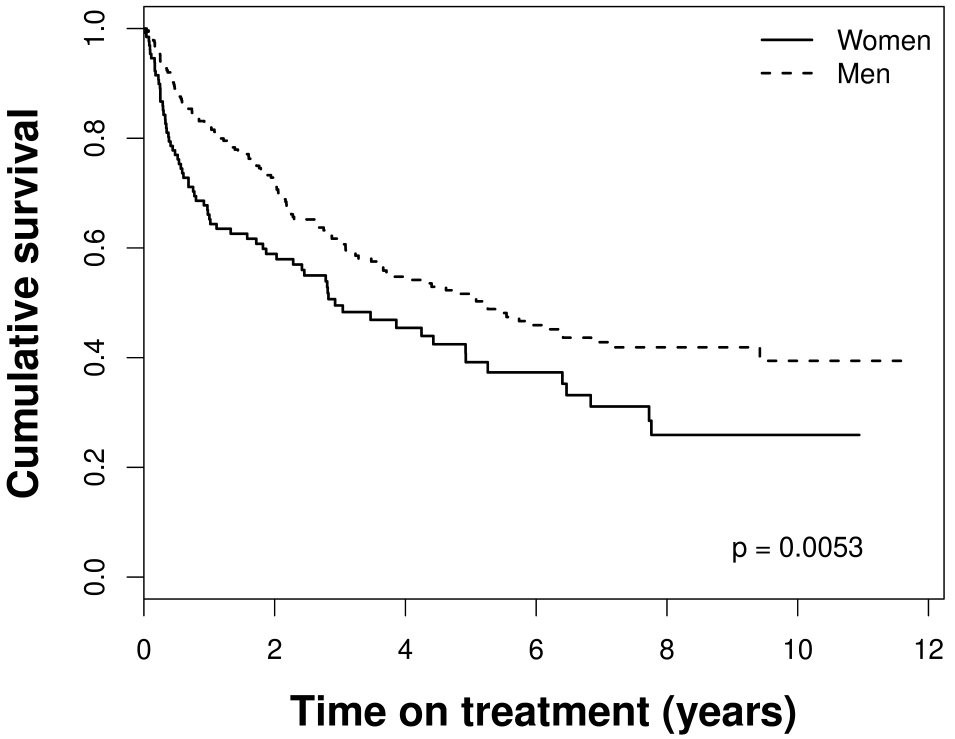

Figure 1. Drug survival of the first tumor necrosis factor inhibitor, stratified by sex.

patients with available covariate data were found during the evaluation of the robustness of our results. A special effort was made to exclude patients with concurrent FM, which is more frequent in women and might have affected our results. However, underreporting of comorbidities and therefore residual confounding cannot be excluded.

Strengths of our investigation include the prospective study design, standardized regular assessments with validated instruments allowing the evaluation of many response variables, and the central scoring of pelvic radiographs for confirmation of AS in all patients.

Despite a comparable disease burden in men and women with AS at initiation of TNFi, a lower effectiveness of anti-TNF agents was found in female patients, confirming previous analyses[10,11,12,14,18].

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