Response to TNF inhibition in male and female patients with ankylosing spondylitis: data from a Swiss cohort

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ABSTRACT

Objectives To investigate sex differences with regard to effectiveness of tumor necrosis factor inhibitors (TNFi) in patients with ankylosing spondylitis (AS).

Methods A total of 440 AS patients (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 ASAS criteria (ASAS20 and ASAS40) as well as Ankylosing Spondylitis Disease Activity Score (ASDAS) improvement and status scores at 1 year. Patients having discontinued the TNFi were considered non-responders. Logistic regression analyses were performed to adjust for important predictors of response.

Results Compared to men, female patients had lower mean C-reactive protein (CRP) levels, a better spinal mobility and more peripheral disease at the start. There was no gender 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 (odds ratio (OR) 0.63, 95% confidence interval (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 0.45, 95% CI 0.22-0.92, p=0.03 for ASAS20 and OR 0.14, 95% CI 0.04-0.40, 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.

INTRODUCTION

While ankylosing spondylitis (AS) has traditionally been considered a disease with male predominance[1], recent investigations have demonstrated a more equitable gender ratio in the nonradiographic form of axial spondyloarthritis (axSpA)[2-4]. Differences in AS disease phenotype that have been demonstrated between men and women comprise more severe spinal radiographic changes in men, while female patients present with more peripheral arthritis, self-reported disease activity, functional impairment, as well as a lower quality of life[5 6]. Moreover, markers of inflammation (elevation of C-reactive protein (CRP) and/or MRI inflammation of the spine) are more frequently associated with male sex[7 8]. There remains a substantially longer diagnostic delay for women, probably due to the fact that the disease is still perceived as being a predominantly male condition and the presence of a later onset of disease in women[9]. It remains unknown, whether all these factors translate into the lower effectiveness of TNFi observed in female AS patients in several studies. Male sex was associated with a better TNFi drug survival in several observational studies[10-12] and was also identified as a predictor of better response in some cohort studies, but not in others[10-14]. The latter inconsistency may be related to the different outcome parameters assessed and to disparities in baseline characteristics across genders in these studies. Age, physical function as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI), enthesitis, elevated baseline CRP and HLA-B27 genotype have been found to be important predictors of response and their combined use to 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]. In addition to results of observational studies, women have also been shown to have less improvement in AS outcome measures in a more recent post hoc analysis of pooled randomized controlled trials of etanercept[18]. In this 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 AS patients after adjustment for important predictors of response in a large prospective observational cohort.

PATIENTS 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 ASAS[19]. Patients were included in the current study if they fulfilled the ASAS criteria for axial spondyloarthritis, 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 were available. Patients with concurrent fibromyalgia at any visit (as indicated by the treating rheumatologist in the comorbidity questionnaire) were excluded (N=9). The study was approved by the Ethics Commission of the Canton of Zurich. 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 months). In the case of TNFi discontinuation before the first outcome assessment, patients were considered non-responders (response/tolerance analysis)[21]. The large window of response assessment was mandated by the structure of SCQM as annual follow-up 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 follow-up) 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 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 parameters were included as variables in a first model: age, BASFI, enthesitis, elevated CRP status and HLA-B27. Smoking, disease duration, BASMI and peripheral arthritis 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 two-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 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 between men and women regarding 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 and Physician Global Assessments were small and not statistically significant.

Treatment response

A follow-up visit at 1 year ±6 months was available for response analyses in 340/440 AS patients (77%). Baseline characteristics of this population, stratified by gender, 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 gender: 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 vs men: 52% versus 63%, odds ratio (OR) 0.63, 95% confidence interval (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).

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 0.45, 95% CI 0.22-0.92, p=0.03 for the ASAS20 responses in model 1 and 2, respectively. Treatment response in women was also found to be diminished in comparison to men in the

adjusted analyses of the other outcomes measured, except for ASAS40, whtere the OR was similarly low as for the other outcomes, but the difference did not reach statistical significance. Gender disparities with regard to 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 was 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, as no baseline disparities across the genders could be detected for BASDAI, BASFI, patient and physician global assessments, as well as for the health-related quality of life. Distinct features mainly contributed to the burden of disease in male and female patients, as we confirm 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 a

non-smoking status 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 genders 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. Men and women are attributed the same values for all co-variables 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, as 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 potentially also explain the limited response to TNF blocking agents in female patients. This issue could not be further investigated here, as in contrast to radiographs, MRIs are not routinely collected in SCQM. Furthermore, with regard to the AS population, there is no need to perform an MRI of the SIJ for diagnostic purposes in the presence of definite radiographic sacroiliac changes in a real-life setting. A further limitation of our study was that follow-up 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 follow-up data were comparable with regard to important baseline characteristics. Lower patient numbers were available for adjusted analyses. Comparable crude response rates in the whole population and in the subset of patients with available covariate data were found during the evaluation of the robustness of our results.

Strengths of our investigation include the prospective study design, standardized regular assessments with validated instruments allowing the evaluation of a multitude of response parameters, the central scoring of pelvic radiographs for confirmation of AS in all patients and the exclusion of patients with known concurrent fibromyalgia.

In conclusion, 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[10-12 14 18].

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Contributors

MH and AC designed the study. All investigators substantially contributed to the acquisition, analysis or interpretation of data. AC wrote the article and all coauthors revised the

manuscript critically for important intellectual content. MH was responsible for the implementation of the statistical analyses. AC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors agreed on the final content of the submitted manuscript.

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Competing interests

Dr. Bernhard has received consulting fees from Merck Sharp & Dohme, Pfizer and Roche. Dr. Ciurea has received consulting and/or speaking fees from AbbVie, Celgene, Eli Lilly, Janssen-Cilag, Merck Sharp & Dohme, Novartis, Pfizer and UCB. Dr. Nissen has received consulting and/or speaking fees from Abbvie, Novartis and Pfizer. Dr. Weber has received speaking fees

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Table 1. Baseline characteristics in women versus men with AS at start of first TNFi

Parameter	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, years	**436**	**27.3 (8.8)**	**25.0 (7.8)**	**0.03**
Symptom duration, years	436	13.2 (10.1)	15.3 (11.4)	0.09
Diagnostic delay, years	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
Patient Global Assessment	407	6.3 (2.4)	6.6 (2.3)	0.25
Physician Global Assessment	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**
Number of 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
On sulfasalazine, %	440	5.5	6.5	0.83
On methotrexate, %	440	5.5	6.5	0.83
On NSAIDs, %	404	96.4	95.1	0.62
Current smokers, %	**393**	**35.1**	**47.3**	**0.02**

Except where indicated otherwise, values are the mean (SD). 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; C-reactive protein (CRP) levels; EQ-5D = EuroQol 5-domain; HLA-B27 = human leucocyte antigen B27; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; modification refers to the inclusion of the plantar fascia in the count; NSAIDs = Nonsteroidal anti-inflammatory drugs; TNFi = Tumour necrosis factor inhibitor.

Table 2. Baseline characteristics of AS patients starting a first TNFi for different outcome analyses.

	A. Response/Tolerance Analysis*				B. Completer analysis**				C. Drug retention analysis			
Parameter	**N**	**Women**	**Men**	**P**	**N**	**Women**	**Men**	**P**	**N**	**Women**	**Men**	**P**
	340	**N = 102**	**N = 238**		**275**	**N = 77**	**N = 198**		**406**	**N = 130**	**N = 276**	
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, years	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, years	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, years	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
Physician Global Assessment	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
Patient Global Assessment	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**
Number of 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
On sulfasalazine, %	340	7.8	6.7	0.82	275	9.1	7.6	0.63	406	6.2	6.2	1.00
On methotrexate, %	340	5.9	5.5	1.00	275	7.8	5.6	0.58	406	4.6	5.8	0.81
On NSAIDs, %	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**

*Response in patients with available outcome at 1 year, patients having discontinued the first TNFi in the meantime being considered non-responders.

Analysis in patients still treated with the first TNF inhibitor at 1 year. Except where indicated otherwise, values are the mean (SD). **A. Patients starting a

first TNFi with available baseline and follow-up visit at 1 year. **B.** Patients still treated with the first TNFi at 1year. **C.** Patients starting a first TNFi with available start and stop dates of drug application. ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; C-reactive protein (CRP) levels; EQ-5D = EuroQol 5-domains; HLA-B27 = human leucocyte antigen B27; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; modification refers to the inclusion of the plantar fascia in the count. NSAIDs = Nonsteroidal anti-inflammatory drugs; TNFi = Tumour necrosis factor inhibitor.

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	0.45	0.22-0.92	0.03
ASAS40	293	40	46	0.79	0.46-1.35	0.37	244	0.60	0.33-1.09	0.10	210	0.52	0.25-1.03	0.06
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	0.39	0.16-0.91	0.03
ASDAS <2.1	284	48	53	0.82	0.48-1.42	0.51	230	0.47	0.24-0.91	0.03	198	0.32	0.14-0.69	0.005
ASDAS improvement ≥2	262	23	32	0.62	0.31-1.19	0.14	228	0.48	0.22-0.99	0.05	196	0.35	0.13-0.84	0.02
ASDAS <1.3	284	18	26	0.65	0.32-1.27	0.22	230	0.29	0.11-0.68	0.007	198	0.14	0.04-0.40	<0.001

[#]Response in patients with available outcome at 1 year, patients having discontinued the first TNFi in the meantime being considered non-responders. ASAS20 and ASAS40 = 20%, respectively 40% improvement according to the Assessment in SpondyloArthritis International Society criteria; ASDAS = Ankylosing Spondylitis Disease Activity Score; OR = odds ratio; 95% CI = 95% confidence interval. TNF = Tumor necrosis factor. *Model 1: adjustment for age, HLA-B27, BASFI, elevated CRP status, enthesitis. **Model 2: additional adjustment for disease duration, BASMI, peripheral arthritis and current smoking.

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	0.42	0.17-1.03	0.06
ASAS40	240	55	55	1.02	0.55-1.89	1.00	204	0.68	0.35-1.30	0.24	175	0.53	0.24-1.14	0.11
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	0.35	0.12-1.02	0.05
ASDAS <2.1	232	65	63	1.07	0.56-2.07	0.88	193	0.56	0.26-1.17	0.12	167	0.29	0.11-0.72	0.009
ASDAS improvement ≥2	219	30	38	0.69	0.33-1.37	0.27	193	0.51	0.23-1.10	0.09	167	0.35	0.13-0.88	0.03
ASDAS <1.3	232	24	31	0.71	0.34-1.42	0.33	193	0.33	0.13-0.80	0.02	167	0.15	0.04-0.44	0.001

[#]Analysis in patients still treated with the first TNF inhibitor at 1 year. ASAS20 and ASAS40 = 20%, respectively 40% improvement according to the Assessment in SpondyloArthritis International Society criteria; ASDAS = Ankylosing Spondylitis Disease Activity Score; OR = odds ratio; 95% CI = 95% confidence interval. TNF = Tumor necrosis factor. *Model 1: adjustment for age, HLA-B27, BASFI, elevated CRP status, enthesitis. **Model 2: additional adjustment for disease duration, BASMI, peripheral arthritis and current smoking.

Figure 1. Drug survival of the first TNFi, stratified by sex.