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2019

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### How to cite

BRULHART, Laure Sophie et al. Ultrasound is not associated with the presence of systemic autoimmunity or symptoms in individuals at risk for rheumatoid arthritis. In: RMD Open, 2019, vol. 5, n° 2, p. e000922. doi: 10.1136/rmdopen-2019-000922

This publication URL: <https://archive-ouverte.unige.ch/unige:135502>

Publication DOI: [10.1136/rmdopen-2019-000922](https://doi.org/10.1136/rmdopen-2019-000922)

# Treatment response and drug retention rates in 24 195 biologic-naïve patients with axial spondyloarthritis initiating TNFi treatment: routine care data from 12 registries in the EuroSpA collaboration

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**Handling editor** Josef S Smolen

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2019-215427>).

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Received 24 March 2019

Revised 17 June 2019

Accepted 13 July 2019

Published Online First

20 August 2019



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**To cite:** Ørnberg LM, Brahe CH, Askling J, et al. *Ann Rheum Dis* 2019;**78**:1536–1544.

## ABSTRACT

**Objective** To study drug retention and response rates in patients with axial spondyloarthritis (axSpA) initiating a first tumour necrosis factor inhibitor (TNFi).

**Methods** Data from 12 European registries, prospectively collected in routine care, were pooled. TNFi retention rates (Kaplan-Meier statistics), Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive disease (<1.3), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) <40 mm and Assessment of SpondyloArthritis International Society responses (ASAS 20/40) were assessed at 6, 12 and 24 months.

**Results** A first TNFi was initiated in 24 195 axSpA patients. Heterogeneity of baseline characteristics between registries was observed. Twelve-month retention was 80% (95% CI 79% to 80%), ranging from 71% to 94% across registries. At 6 months, ASDAS Inactive disease/BASDAI<40 rates were 33%/72% (LUNDEX-adjusted: 27%/59%), ASAS 20/40 response rates 64%/49% (LUNDEX-adjusted 52%/40%). In patients initiating first TNFi after 2009, 6097 patients was registered to fulfil ASAS criteria for axSpA, 2935 was registered to fulfil modified New York Criteria for Ankylosing Spondylitis and 1178 patients was registered as having non-radiographic axSpA. In nr-axSpA patients, we observed lower 12-month retention rates (73% (70%–76%)) and lower 6-month LUNDEX adjusted response rates (ASDAS Inactive disease/BASDAI40 20%/50%, ASAS 20/40 45%/33%). For patients initiating first TNFi after 2014, 12-month retention rate, but not 6-month response rate, was numerically higher compared with patients initiating TNFi in 2009–2014.

**Conclusion** A large European database of patients with axSpA initiating a first TNFi treatment in routine care, demonstrated that 27% of patients achieved ASDAS inactive disease after 6 months, while 59% achieved BASDAI <40. Four of five patients continued treatment after 1 year.

## Key messages

### What is already known about this subject?

- Single countries have reported effectiveness of tumour necrosis factor inhibitor (TNFi) treatment in axial spondyloarthritis (axSpA), but the generalisability of the findings is unknown.

### What does this study add?

- This study of 24 195 European axSpA patients in a pooled dataset offered large-scale real-world evidence on the effectiveness of TNFi across 12 European countries.
- Overall, ~1/4 of patients achieved ASDAS inactive disease after 6 months and 80% were still receiving the same TNFi after 1 year.
- Patients with non-radiographic AxSpA showed numerically lower ASDAS inactive disease rates (1/5 at 6 months) and 12-month retention rates (73%).

### How might this impact on clinical practice or future developments?

- The EuroSpA collaboration offers unprecedented opportunities for providing real-world evidence on European patients with axSpA, including drug effectiveness, predictors thereof and differences between countries.

## INTRODUCTION

Tumour necrosis factor inhibitors (TNFi) improve symptoms of axial spondyloarthritis (axSpA), such as inflammatory back pain, stiffness and range of motion.<sup>1–3</sup> Their effects have been demonstrated in randomised controlled trials (RCTs) and TNFi are now an essential part of axSpA treatment.<sup>4–7</sup>

However, in contrast to the RCTs with strict inclusion and exclusion criteria, a more heterogeneous group of patients with a broad spectrum of various comorbidities, concomitant medications and atypical disease manifestations is treated in routine care. Thus, up to 80% of patients receiving TNFi in routine care would not have been eligible to be enrolled in the RCTs that led to approval of the agents.<sup>8</sup> This observation emphasises the need for real-world observational studies as a valuable supplement to RCTs.

To date, single countries have reported real-world effectiveness of TNFi treatments in axSpA.<sup>9–11</sup> Investigation of characteristics of patients exposed to TNFi, treatment adherence and response rates of TNFi across countries would improve our knowledge of the effectiveness of TNFi treatment in axSpA patients treated in routine care.

The EuroSpA collaboration is a research network of 15 European registries that has been created to strengthen research on patients with spondyloarthritis in the real-world setting. In this first study of axSpA patients in which 12 of the registries participated, we aimed to investigate retention and response rates among TNFi-naïve axSpA patients initiating a first TNFi treatment. Analyses were performed in a pooled dataset of axSpA patients across all registers, in data from individual registries as well as in subgroups of patients registered as fulfilling Assessment of Spondyloarthritis International Society (ASAS) criteria for axSpA, fulfilling modified New York Criteria for Ankylosing Spondylitis (AS) and as having non-radiographic axSpA.<sup>1–3</sup> We also investigated potential heterogeneity of patient characteristics between registries at treatment initiation.

## METHODS

### The EuroSpA research collaboration

The present study included secondary use of data on patients registered with an axSpA diagnosis from 12 European registries up to 2018 and data were uploaded from the following registries: ARTIS (Sweden), DANBIO (Denmark), SCQM (Switzerland), ATTRA (Czech Republic), TURKBIO (Turkey), NOR-DMARD (Norway), ROB-FIN (Finland), Reuma.pt (Portugal), RRBR (Romania), BIOBADASER (Spain), biorx.si (Slovenia) and ICEBIO (Iceland).

### Data sources

In all registries, data are collected prospectively as part of routine clinical practice. Based on a predefined study protocol, a list of study variables including definitions for each variable was sent to data managers in each registry. The data managers created anonymised datasets and uploaded these through secure Virtual Private Network pipelines to the EuroSpA server. Statistical analyses were predefined in the study protocol and statistical analysis plan.

### Patients

Patients were included if they had a diagnosis of axSpA as judged by the treating rheumatologist, were aged  $\geq 18$  years at diagnosis, had received treatment with at least one TNFi after diagnosis and were registered with start and (if relevant) stop dates of TNFi. We conducted analyses separately for patients initiating a first TNFi since registry start, and for three subcohorts of patients initiating a first TNFi after 1 January 2009 with available registration of classification criteria: patients registered to fulfil ASAS criteria for axSpA (ASAS cohort), patients registered to fulfil the modified New York criteria for AS (NY cohort) and patients registered to fulfil ASAS criteria

and to NOT fulfil the modified New York criteria for AS (nr-axSpA cohort).

### Clinical variables

Baseline variables included age, gender, human leucocyte antigen B27 (HLA-B27) status, body mass index, time since diagnosis, smoking status, current treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) as well as TNFi agent. At baseline and after 6, 12 and 24 months' follow-up, the following disease scores were included: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)<sup>12</sup> and Bath Ankylosing Spondylitis Functional Index (BASFI), both on a 0–100 mm scale.<sup>13</sup> Furthermore, fatigue and global scores on visual analogue scales (VAS) were obtained as well as the components required for calculation of the Ankylosing Spondylitis Disease Activity Score (ASDAS).<sup>14</sup> The 6-month visit was defined as a registered visit from 90 to 270 days after baseline, the 12-month visit as a registered visit from 271 to 545 days after baseline and a 24-month visit as a registered visit from 546 to 910 days after baseline.

### Retention rates

The treatment period (time on drug) was defined as the number of days between the registered date of treatment start and the registered stop date for the individual patients. A treatment without a registered stop date was assumed to have been discontinued if a new biologic DMARD (bDMARD) was recorded in the registry and the stop date was defined as the date of next bDMARD start. If no new bDMARD was registered the treatment was assumed to have ended 12 months after the last registered visit. If the same drug was restarted within 3 months of the recorded treatment stop date, with no other bDMARD recorded in-between, the treatment periods were considered as one period.

Retention rates were calculated as the percentage of patients still on TNFi 6, 12 and 24 months after treatment start. Observations were censored by: (1) the date of data extraction; (2) date of death; or (3) end of registry follow-up, whichever came first; (4) withdrawal from treatment for other reasons than lack of efficacy (LOE) and adverse events (AE), that is, remission or other reasons such as planning for pregnancy.

### Treatment response

At 6, 12 and 24 months' follow-up, clinical response was evaluated as achievement of ASDAS inactive disease ( $<1.3$ ), BASDAI  $<40$  or achievement of ASAS 20/40 response.

### Primary and secondary outcomes

The primary study outcome was the overall 12-month TNFi drug retention rate. Secondary outcomes were overall 6 and 24 months' retention rates and proportions of axSpA patients achieving ASDAS inactive disease, BASDAI  $<40$  and ASAS 20/40 response at 6, 12 and 24 months. Explorative outcomes were retention and response rates in the individual registries at 6, 12 and 24 months, and differences in retention and crude and LUNDEX-adjusted response rates by calendar year.

### Ethics

When required, the registries obtained the necessary approvals from national data protection agencies and/or local research ethics boards prior to data transfer. Data from the participating

registries were sent to the coordinating centre in accordance with legal, compliance and regulatory requirements. This study was designed and is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines and with the ethical principles according to the Declaration of Helsinki.

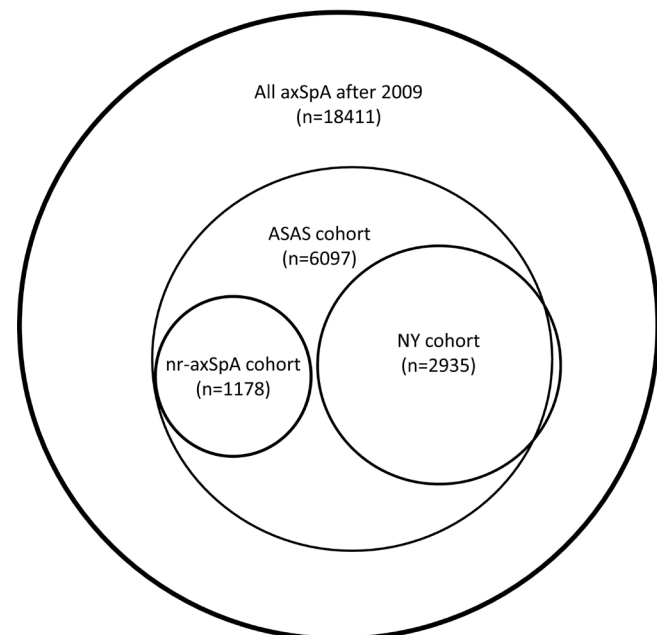
### Statistical analysis

R V.3.4.3 software was used for statistical analyses. All calculations were based on observed data. No imputation of missing data was performed. The number of patients with available data at baseline and follow-up are shown in table 1 and online supplementary tables S1-S4 and S6-S11.

Descriptive statistics (median, IQR and/or percentage) were applied for demographics and patient characteristics. Comparisons between individual registries and baseline characteristics were tested with analysis of variance (ANOVA). For baseline variables that showed significant heterogeneity, pairwise comparison was performed with  $\chi^2$  tests (for categorical variables), Mann-Whitney tests (for non-normally distributed continuous data) and two-tailed Student's t-test (for normally distributed continuous data).

TNFi retention rates (in the pooled cohort and stratified per registry) were investigated by Kaplan-Meier estimation. Age-standardised and gender-standardised drug retention rates were calculated by using the WHO European standard population.<sup>15</sup>

Response rates (crude and adjusted according to LUNDEX<sup>16</sup>) were calculated for ASDAS inactive disease, BASDAI <40 and ASAS 20/40 response. Differences between registries were tested by  $\chi^2$  test for crude and LUNDEX-adjusted response rates and logrank for retention rates.



**Figure 1** VENN diagram of all axSpA patients starting treatment after 2009. axSpA, axial spondyloarthritis; ASAS cohort, patients registered to fulfill the Assessment of Spondyloarthritis International Society (ASAS) criteria for axSpA; Ny cohort, patients registered to fulfill the Modified New York criteria for Ankylosing Spondylitis (AS); nr-axSpA cohort, patients registered to fulfill the ASAS criteria for axSpA and NOT fulfill the Modified New York criteria for AS.

## RESULTS

### Patient characteristics

A total of 24 195 patients with axSpA initiating their first TNFi were identified from the 12 participating registries and data were pooled. Registration of classification criteria was available in 35% of patients, and the following subcohorts were identified: ASAS cohort (n=6097), NY cohort (n=2935) and nr-axSpA cohort (n=1178) (figure 1).

Most patients were prescribed infliximab (28%), adalimumab (29%) or etanercept (25%), while 14% were treated with golimumab and 5% with certolizumab (table 1). During the study period, some drugs, for example, infliximab, were used off label in the treatment of nr-axSpA. Thirty-one per cent of patients received csDMARDs. At baseline, median (IQR) time since diagnosis was 2 (1-9) years, BASDAI 59 mm (44-72) and BASFI 46 mm (26-66).

Table 2 shows baseline variables for the 12 registries. Statistically (and clinically) significant differences between the registries were observed for all baseline variables (ANOVA;  $p < 0.001$ ). Subsequent pairwise comparison of registries showed statistically significant differences for most baseline variables (data not shown). Patients with AS (fulfilling modified New York criteria) compared with nr-axSpA patients were more often men (67% vs 52%), had longer time since diagnosis (3 (1-10) vs 1 (0-3) years) and higher CRP (13 (5-27) vs 7 (2-19) mg/L). Median BASDAI scores at first TNFi initiation were very similar (66 (52-77) vs 65 (50-78), respectively).

### TNFi retention rates at 6, 12 and 24 months

For the entire cohort, the 12-month TNFi retention rate was 80% (95% CI 79% to 80%). Corresponding 12-month retention rates for patients in the ASAS cohort, NY cohort and nr-axSpA cohort were 81% (80% to 82%), 83% (82% to 85%) and 73% (70% to 76%), respectively. At 6/24 months, retention rates for all patients were 88% (87% to 88%) / 73% (72% to 73%), for ASAS cohort 89% (88% to 90%) / 74% (73% to 76%), for NY cohort 90% (89% to 91%) / 76% (74% to 78%) and for nr-axSpA cohort 84% (82% to 86%) / 64% (62% to 67%) (table 3).

The 12-month retention rate in the individual registries differed significantly ( $p < 0.001$ , logrank) and ranged from 71% to 94% (table 4 and figure 2). Retention rates in the individual registries after 6 and 24 months ranged from 81% to 98% and 62% to 92% ( $p < 0.001$ , logrank), respectively.

Standardised retention rates (age and gender) for the individual registries at 6, 12 and 24 months were similar to the non-standardised retention rates (table 4).

Over calendar years, retention rates tended to decrease from before 2009 to 2009 to 2014 and to increase again after 2014 (online supplementary table S6).

### Achievement of ASDAS inactive disease, BASDAI <40 and ASAS 20/40 response at 6, 12 and 24 months

Overall, ASDAS inactive disease was achieved in 33%, 35% and 38% of the patients at 6, 12 and 24 months, respectively. For BASDAI <40 the proportions were 72%, 75% and 77%, whereas ASAS 20/40 response rates were achieved in 64%/49% at 6 months, 67%/53% at 12 months and 68%/54% at 24 months. Corresponding LUNDEX adjusted rates at 6, 12 and 24 months were 27%, 24% and 19% for ASDAS inactive disease, 59%, 51% and 38% for BASDAI <40. LUNDEX adjusted ASAS 20/40 response rates were 52%/40% at 6

**Table 1** Baseline characteristics of all patients and the axSpA subcohorts

	All patients		ASAS cohort*		NY cohort†		nr-axSpA cohort‡	
	No of patients with available data, n	Median (IQR) or percentage	No of patients with available data, n	Median (IQR) or percentage	No of patients with available data, n	Median (IQR) or percentage	No of patients with available data, n	Median (IQR) or percentage
Age, years	24195	41 (33–50)	6097	41 (33–50)	2935	43 (34–52)	1178	39 (31–48)
Male	24195	61%	6097	63%	2935	67%	1178	52%
HLA-B27	12620	74%	5645	76%	2595	70%	1104	69%
BMI, kg/m <sup>2</sup>	10418	26 (23–29)	4699	26 (23–29)	2266	26 (23–29)	753	25 (23–29)
Concomitant csDMARD	23984	31%	6002	29%	2865	26%	1169	25%
Time since diagnosis, years	19091	2 (1–9)	5971	2 (1–8)	2884	3 (1–10)	1155	1 (0–3)
Current smoking	21049	23%	5755	27%	2822	27%	1121	26%
Infliximab	6874	28%	1143	19%	580	20%	194	16%
Etanercept	6034	25%	1165	19%	647	22%	230	20%
Adalimumab	6936	29%	2176	36%	1050	36%	410	35%
Certolizumab	1107	5%	240	4%	77	3%	60	5%
Golimumab	3244	14%	1373	23%	581	20%	284	24%
Start before 2009	5784	24	0	0	0	0	0	0
Start 2009–2011	5061	21	1586	26	941	32	345	29
Start 2012–2014	6092	25	2123	35	932	32	500	42
Start 2015–2017	7258	30	2388	39	1062	36	333	28
CRP, mg/L	18552	10 (4–23)	5159	13 (5–26)	2446	13 (5–27)	1003	7 (2–19)
CRP >10 mg/L	18552	48%	5159	56%	2446	56%	1003	40%
BASDAI, mm	14442	59 (44–72)	5014	64 (51–76)	2442	66 (52–77)	994	65 (50–78)
BASMI, mm	4551	24 (10–40)	1937	20 (10–40)	1037	30 (10–50)	605	20 (10–30)
BASFI, mm	11548	46 (26–66)	4187	51 (33–69)	1840	53 (34–70)	762	48 (29–68)
ASDAS, units	7678	3.6 (2.9–4.2)	3139	4.0 (3.3–4.6)	1394	4.1 (3.3–4.7)	561	3.9 (3.1–4.6)
VAS pain, mm	15332	65 (45–80)	4249	70 (52–82)	1927	75 (58–90)	911	70 (52–86)
VAS fatigue, mm	10718	69 (49–80)	3650	70 (51–85)	1434	77 (60–90)	853	72 (51–86)

Data are as observed, median (IQR) or percentage.

\*Patients registered as fulfilling the ASAS criteria for axSpA, initiating treatment after 2009.

†Patients registered as fulfilling the modified New York Criteria for ankylosing spondyloarthritis (AS), initiating treatment after 2009.

‡Patients registered to fulfil the ASAS criteria for axSpA and to NOT fulfil the modified New York criteria for AS (nr-axSpA), initiating treatment after 2009.

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; INF, infliximab; TNFi, tumour necrosis factor inhibitor; VAS, visual analogue scale; csDMARD, conventional synthetic disease-modifying antirheumatic drug.

months, 46%/36% at 12 months and 34%/27% at 24 months (table 4).

For the subcohorts of patients in the ASAS, NY and nr-axSpA cohort, ASDAS inactive disease response rates at 6, 12 and 24 months were 30%, 25% and 26%, respectively, and corresponding LUNDEX-adjusted rates were 25%, 21% and 20%. BASDAI <40 for the three subgroups of patients at 6, 12 and 24 months were 73%, 71% and 64%, and corresponding LUNDEX adjusted rates were 60%, 60% and 50%.

The 6-month response rates (ASDAS inactive disease and BASDAI <40) in the individual registries ranged from 29% to 53% (LUNDEX adjusted from 17% to 46%) and 61% to 86% (LUNDEX adjusted from 50% to 72%), respectively (p<0.001) (table 4).

The crude and LUNDEX adjusted response rates for BASDAI <40, ASDAS inactive disease and ASAS 20/40 did not show any consistent differences when comparing patients initiating first TNFi before 2009, from 2009 to 2014 or after 2014 (online supplementary S6).

The relation between four selected baseline parameters in different countries and LUNDEX-adjusted response rate (BASDAI ≤40) at 6 months were explored (online supplementary figure S1).

Details about number of patients are found in online supplementary S1, S2, S3 and S4.

### Reasons for withdrawal of TNFi treatment

During 24 months of follow-up, a total of 5673 patients (23%) withdrew from treatment. Of these, 3654 patients stopped due

to LOE and 2019 due to AE. For patients who withdrew during the 24 months' follow-up period, the median (IQR) time to withdrawal was 7 months (4–13).

For patients in the ASAS, NY and nr-axSpA cohort, the reasons for withdrawal and median time to withdrawal were comparable to the pooled cohort (online supplementary S5).

### DISCUSSION

This is the first study of patients with axSpA initiating a first TNFi in routine care, using data from the EuroSpA research collaboration and includes data from 12 countries and over 24 000 patients.

Overall, 80% of patients remained on the TNFi 12 months after treatment start. This is comparable to retention rates reported for earlier observational studies of patients with axSpA or AS initiating treatment with a TNFi. In a Swedish study from 2014 of 112 patients with nr-axSpA (patients fulfilling modified New York criteria for AS were excluded), the 12-month retention rate was 76% and 2-year retention rate 65%.<sup>17</sup> In a study from 2010 of 842 Danish TNFi naive patients with AS, 12-month and 24-month retention rates were 74% and 63%, respectively.<sup>18</sup> The 12-month retention rates in individual registries varied from 71% to 94%. Different prescription patterns across countries may explain part of this variability. Despite international recommendations regarding treatment strategies,<sup>19</sup> they may be overruled by national guidelines. These guidelines may have changed over time. Currently, an overview of the guidelines in individual European countries and the changes therein over time does not exist. Examples of differences between countries are different initial doses and/or step up

**Table 2** Baseline characteristics of all axSpA patients, stratified by registry

Country	ARTIS		BIOBADASER		Biorx.si		DANBIO		ICEBIO		NOR-DMARD		Reuma.pt		RRBR		ROB-FIN		SCQM		TURKBIO		ATTRA	
	Sweden	Spain	Slovenia	Denmark	Iceland	Norway	Portugal	Romania	Finland	Switzerland	Turkey	Czech Republic												
All patients (n)	6945	662	615	3897	316	1562	1156	672	1367	2578	2095	2330												
ASAS cohort* (n)	NA	NA	503	1229	30	113	700	672	56	1212	351	1231												
NY cohort† (n)	NA	NA	467	512	30	38	563	524	NA	559	242	NA												
nr-axSpA cohort‡ (n)	NA	NA	37	544	4	68	82	148	NA	221	74	NA												
Age, years	41 (32–51)	45 (38–55)	45 (36–55)	41 (32–50)	43 (35–53)	40 (33–50)	41 (34–51)	43 (34–52)	41 (33–51)	42 (33–51)	38 (31–46)	39 (33–48)												
Year of first patient initiating TNFi	1999	2000	2002	2000	2001	2001	2001	2015	2000	2002	2001	2002												
Male	58%	69%	64%	61%	66%	60%	56%	74%	59%	53%	60%	72%												
HLA-B27	NA	81%	80%	71%	92%	82%	77%	51%	87%	64%	62%	91%												
BMI, kg/m <sup>2</sup>	NA	26 (24–30)	26 (23–29)	26 (23–29)	26 (24–29)	25 (23–29)	25 (23–29)	26 (24–29)	26 (23–29)	25 (23–29)	27 (24–30)	26 (23–29)												
Concomitant csDMARD, pct	33%	30%	15%	27%	22%	18%	42%	42%	72%	19%	20%	41%												
Time since diagnosis, years	1 (0–7)§	5 (1–13)	5 (1–12)	1 (0–6)	3 (0–11)	4 (1–14)	4 (1–10)	3 (1–10)	4 (1–11)	1 (0–7)	3 (1–7)	5 (2–10)												
Current smoking	12%	31%	22%	33%	24%	29%	29%	12%	23%	25%	41%	24%												
Infliximab	34%	25%	15%	35%	83%	18%	22%	17%	30%	21%	27%	23%												
Etanercept	29%	20%	23%	14%	8%	32%	27%	27%	33%	25%	29%	22%												
Adalimumab	27%	30%	43%	29%	2%	18%	31%	36%	27%	33%	28%	37%												
Certolizumab	3%	7%	1%	7%	0%	19%	1%	0%	1%	2%	5%	2%												
Golimumab	10%	19%	17%	15%	7%	12%	18%	20%	8%	19%	11%	15%												
Start before 2009	25%	23%	18%	25%	36%	26%	18%	0%	43%	27%	11%	23%												
Start 2009–2011	21%	9%	29%	22%	16%	24%	24%	0%	25%	25%	15%	22%												
Start 2012–2014	25%	15%	35%	26%	21%	30%	26%	0%	20%	26%	31%	26%												
Start 2015–2017	29%	53%	18%	27%	28%	20%	32%	100%	12%	22%	43%	28%												
CRP, mg/L	8 (3–21)	3 (1–9)	11 (3–25)	8 (3–19)	7 (3–19)	9 (3–15)	11 (4–26)	24 (16–41)	8 (3–20)	7 (3–15)	12 (4–26)	20 (12–32)												
CRP >10 mg/L	43%	22%	51%	42%	38%	33%	52%	84%	42%	33%	55%	80%												
BASDAI, mm	56 (40–69)	55 (43–70)	69 (57–80)	61 (47–73)	60 (46–76)	50 (33–65)	62 (49–76)	74 (66–82)	39 (14–58)	57 (42–71)	49 (35–62)	65 (52–76)												
BASFI, mm	38 (20–59)	NA	58 (40–73)	49 (31–67)	43 (32–58)	NA	61 (40–75)	NA	27 (7–49)	38 (19–60)	31 (17–51)	54 (38–70)												
BASMI, mm	NA	NA	NA	30 (10–40)	20 (10–30)	NA	40 (28–54)	NA	NA	20 (10–30)	30 (10–50)	NA												
ASDAS, units	3.1 (2.5–3.8)	3.4 (2.6–4.0)	NA	3.5 (2.9–4.2)	3.7 (3.2–4.2)	NA	3.7 (3.1–4.3)	4.6 (4.2–5.0)	2.8 (2.0–3.5)	NA	3.5 (2.9–4.0)	4.0 (3.5–4.5)												
VAS pain, mm	62 (43–75)	NA	70 (50–80)	66 (49–78)	65 (46–78)	50 (31–68)	50 (10–60)	90 (80–100)	85 (31–72)	70 (50–80)	71 (51–80)	70 (50–80)												
VAS fatigue, mm	63 (36–78)	NA	NA	11 (52–84)	59 (45–80)	85 (30–75)	NA	90 (80–90)	NA	70 (50–80)	70 (50–75)	65 (50–80)												

Data are as observed, median (IQR) or percentage.

\* Patients registered as fulfilling the ASAS criteria for axSpA, initiating treatment after 2009.

† Patients registered as fulfilling the modified New York Criteria for ankylosing spondyloarthritis (AS), initiating treatment after 2009.

‡ Patients registered to fulfil the ASAS criteria for axSpA and to NOT fulfil the modified New York criteria for AS (nr-axSpA), initiating treatment after 2009.

§ Time since inclusion in ARTIS.

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; TNFi, tumour necrosis factor inhibitor; VAS, visual analogue scale; csDMARD, conventional synthetic disease-modifying antirheumatic drug.

**Table 3** Retention and response rates in patients with axial spondyloarthritis

	All patients		ASAS cohort*		NY cohort†		nr-axSpA cohort‡	
	Retention rates		Retention rates		Retention rates		Retention rates	
6 months (95% CI)	88% (87% to 88%)		89% (88% to 90%)		90% (89% to 91%)		84% (82% to 86%)	
12 months (95% CI)	80% (79% to 80%)		81% (80% to 82%)		83% (82% to 85%)		73% (70% to 76%)	
24 months (95% CI)	73% (72% to 73%)		74% (73% to 76%)		76% (74% to 78%)		64% (62%–67%)	
	Response rates		Response rates		Response rates		Response rates	
	Crude§	LUNDEX adjusted ¶	Crude§	LUNDEX adjusted¶	Crude§	LUNDEX adjusted¶	Crude§	LUNDEX adjusted¶
ASDAS inactive disease at 6 months	33%	27%	30%	25%	25%	21%	26%	20%
ASDAS inactive disease at 12 months	35%	24%	33%	23%	29%	21%	31%	19%
ASDAS inactive disease at 24 months	38%	19%	38%	18%	32%	16%	37%	15%
BASDAI <40 at 6 months	72%	59%	73%	60%	71%	60%	64%	50%
BASDAI <40 at 12 months	75%	51%	76%	52%	73%	52%	70%	43%
BASDAI <40 at 24 months	77%	38%	79%	37%	76%	37%	71%	29%
ASAS 20/40 at 6 months	64%/49%	52%/40%	68%/54%	56%/45%	64%/48%	54%/41%	57%/42%	45%/33%
ASAS 20/40 at 12 months	67%/53%	46%/36%	70%/57%	48%/39%	66%/52%	47%/37%	63%/49%	39%/30%
ASAS 20/40 at 24 months	68%/54%	34%/27%	73%/59%	34%/28%	67%/51%	33%/25%	69%/53%	28%/22%

Data are as observed, median (IQR) or percentage.

\*Patients registered as fulfilling ASAS criteria, initiating treatment after 2009.

†Patients registered as fulfilling the modified New York Criteria for AS, initiating treatment after 2009.

‡Patients registered to fulfil the ASAS criteria for axSpA and to NOT fulfil the modified New York criteria for AS (nr-axSpA), initiating treatment after 2009.

§Crude value: the fraction responding of those still on drug at 6, 12 and 24 months, respectively.

¶LUNDEX adjusted: crude value adjusted for drug retention.

ASAS, Assessment of Spondylo Arthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

strategies,<sup>20–22</sup> comedication with csDMARDs<sup>23–25</sup> and mandatory elevation of CRP or evidence of inflammation on MRI for patients with nr-axSpA.<sup>26</sup> Those differences in access to therapy and treatment guidelines between countries probably account for some of the variation in both baseline variables and treatment outcomes observed in the present study.

Further, patients selected to receive their first TNFi varied across the countries, which was not unexpected. For instance, the disease activity (BASDAI) at baseline in individual countries varied from 39 to 74mm. Moreover, HLA-B27-positive patients at baseline varied from 51% to 92%, and the percentage of patients treated with concomitant csDMARD varied from 15% to 72%. Although no consistent pattern was found, it appeared that countries with a high proportion of HLA-B27-positive patients and a high proportion of patients receiving concomitant csDMARDs achieved higher LUNDEX-adjusted BASDAI remission rates. Further studies of the predictive value of baseline characteristics in individual countries for crude and LUNDEX-adjusted response and remission rates are needed. Interestingly, adjustment for age and gender did not change retention and response rates substantially.

Different response measures have been applied in previous studies, which makes comparisons difficult. A Danish study of 842 Danish TNFi naive patients with AS evaluated drug effectiveness by reduction in BASDAI of at least 50% or >20mm compared with baseline according to the ASAS guidelines (BASDAI 50%/20mm response) and reported a response rate of 63%.<sup>18</sup> Landewe *et al* investigated ASAS20 response in 325 axSpA patients treated with certolizumab. At week 12, ASAS20

response was 58%–64%, and no differences were observed between patients with AS and nr-axSpA.<sup>27</sup> This is in line with our findings where ASAS20 response at 6-month follow-up was 64%. The study of Sieper *et al* evaluated the efficacy of adalimumab in 185 patients who fulfilled ASAS criteria.<sup>28</sup> They found 36% of patients achieved ASAS40 at week 12, which is comparable to the percentage of patients achieving ASAS40 in our pooled population.

The large number of patients allowed us to identify and analyse data on three subcohorts of axSpA patients, who had started treatment after 2009. These subcohorts were patients who were explicitly registered as (1) fulfilling the ASAS criteria for axSpA (ASAS cohort) or (2) the modified New York criteria for AS (NY cohort). The nr-axSpA cohort was constructed of patients registered to fulfil ASAS criteria and to NOT fulfil the Modified New York criteria. This information was only available in a minority of patients, which explains the lower patient numbers in the subcohorts. The subcohorts were investigated to clarify if they displayed marked differences in retention and response rates. Interestingly, nr-axSpA subcohort had lower retention rates at 12 months. Furthermore, we found numerically lower LUNDEX-adjusted response rates (BASDAI <40 and ASAS 20/40 response at 6 months) for nr-axSpA patients compared with the other subcohorts. This observation may reflect that the subcohort of nr-axSpA patients include some patients with a less certain diagnosis, which may consequently respond poorly and discontinue their TNFi more frequently. However, our data showed no differences in crude response rates.

**Table 4** Retention rates at 6, 12 and 24 months and response rates at 6 months stratified by registry

Registry	All patients		ASAS cohort*		NY cohort†		nr-axSpA cohort‡		All patients			
	Retention rates (6/12/24 months), pct		Retention rates (6/12/24 months), pct		Retention rates (6/12/24 months), pct		Retention rates (6/12/24 months), pct		Rates of ASDAS inactive disease (6 months)		Rates of BASDAI <40 (6 months)	
	95% CI		95% CI		95% CI		95% CI		Crude§	LUNDEX adjusted¶	Crude¶	LUNDEX adjusted**
ARTIS	87/79/71	(86 to 88)/ (78 to 80)/ (69 to 72)	NA	NA	NA	NA	NA	NA	41%	33%	71%	56%
BIOBADASAR	92/86/79	(90 to 94)/ (83 to 89)/ (76 to 83)	NA	NA	NA	NA	NA	NA	20%	17%	61%	52%
Biorx.si	93/86/80	(90 to 95)/ (83 to 89)/ (76 to 83)	91/83/75	(88 to 93)/ (80 to 86)/ (71 to 79)	91/83/76	(88 to 94)/ (80 to 87)/ (72 to 80)	89/77/68	(79 to 100)/ (65 to 93)/ (53 to 86)	NA	NA	67%	61%
DANBIO	81/71/62	(80 to 82)/ (70 to 73)/ (61 to 64)	80/70/59	(78 to 83)/ (68 to 73)/ (57 to 62)	83/75/65	(80 to 87)/ (71 to 79)/ (61 to 70)	79/66/55	(75 to 82)/ (62 to 70)/ (51 to 60)	29%	22%	64%	48%
ICEBIO	89/79/70	(86 to 93)/ (74 to 84)/ (65 to 75)	80/70/63	(67 to 96)/ (55 to 88)/ (48 to 83)	80/70/63	(67 to 96)/ (55 to 88)/ (48 to 83)	75/50/50	(43 to 100)/ (19 to 100)/ (19 to 100)	42%	36%	74%	63%
NOR-DMARD	82/72/63	(80 to 84)/ (70 to 75)/ (61 to 66)	92/86/80	(87 to 97)/ (80 to 93)/ (72 to 87)	95/92/84	(88 to 100)/ (84 to 100)/ (73 to 97)	90/81/75	(83 to 97)/ (72 to 91)/ (65 to 86)	NA	NA	76%	61%
Reuma.pt	93/87/82	(91 to 94)/ (85 to 89)/ (79 to 84)	94/87/82	(92 to 96)/ (84 to 90)/ (79 to 85)	94/88/82	(92 to 96)/ (86 to 91)/ (79 to 86)	92/78/69	(87 to 98)/ (69 to 88)/ (59 to 81)	23%	20%	64%	57%
ROB-FIN	95/92/89	(94 to 96)/ (91 to 94)/ (87 to 91)	91/87/75	(83 to 99)/ (78 to 96)/ (63 to 90)	NA	NA	NA	NA	53%	46%	79%	68%
RRBR	98/94/92	(97 to 99)/ (92 to 96)/ (89 to 95)	98/94/92	(97 to 99)/ (92 to 96)/ (89 to 95)	98/93/91	(97 to 99)/ (91 to 96)/ (88 to 94)	99/97/95	(98 to 100)/ (94 to 100)/ (91 to 99)	22%	18%	86%	69%
SCQM	83/74/66	(82 to 85)/ (73 to 76)/ (65 to 68)	83/75/68	(81 to 86)/ (72 to 77)/ (65 to 71)	86/77/69	(83 to 88)/ (74 to 81)/ (65 to 73)	80/71/66	(75 to 86)/ (65 to 77)/ (60 to 73)	NA	NA	62%	50%
TURKBIO	92/85/77	(91 to 93)/ (83 to 86)/ (75 to 79)	89/82/75	(85 to 92)/ (78 to 86)/ (70 to 80)	89/84/78	(85 to 93)/ (80 to 90)/ (73 to 84)	87/76/67	(80 to 95)/ (66 to 87)/ (56 to 81)	27%	22%	79%	65%
ATTRA	93/88/83	(92 to 94)/ (87 to 90)/ (82 to 85)	94/88/84	(92 to 95)/ (87 to 90)/ (82 to 86)	NA	NA	NA	NA	38%	34%	81%	72%

Data are as observed, median (95% CI); ARTIS (Sweden); BIOBADASAR (Spain); Biorx.si (Slovenia); DANBIO (Denmark); ICEBIO (Iceland); NOR-DMARD (Norway); Reuma.pt (Portugal); ROB-FIN (Finland); RRBR (Romania); SCQM (Switzerland); TURKBIO (Turkey); ATTRA (Czech Republic).

\*Patients registered as fulfilling ASAS criteria, initiating treatment after 2009.

†Patients registered as fulfilling the modified New York Criteria for AS, initiating treatment after 2009.

‡Patients registered to fulfil the ASAS criteria for axSpA and to NOT fulfil the modified New York criteria for AS (nr-axSpA), initiating treatment after 2009.

§Standardised (age and gender) drug retention rates.

¶Crude value: the fraction responding of those still on drug at 6, 12 and 24 months, respectively.

\*\*LUNDEX adjusted: crude value adjusted for drug retention.

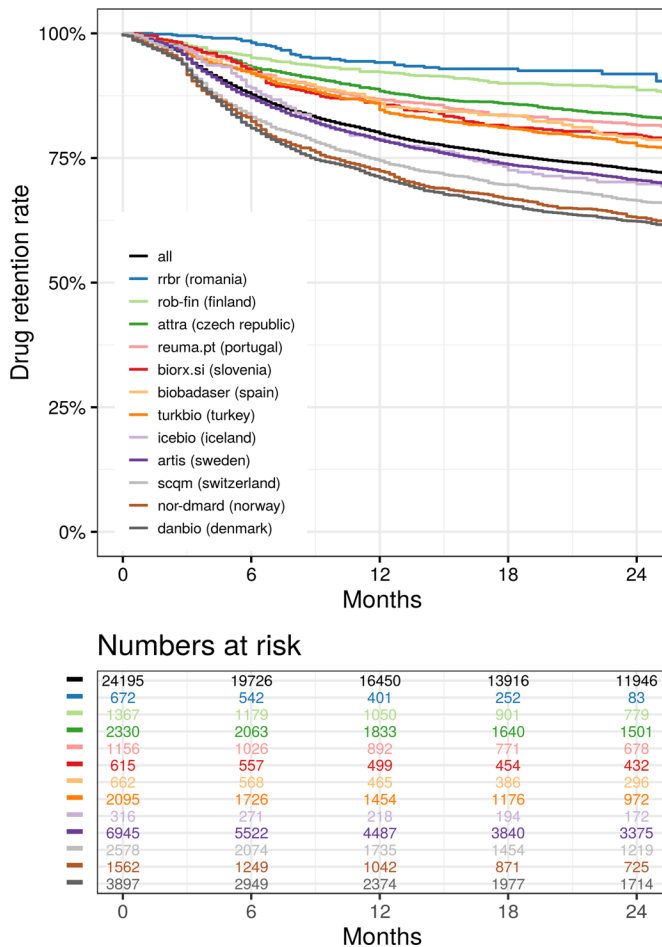
Also, differences in baseline characteristics were found between the subgroups of patients registered with AS according to New York criteria and patients with nr-axSpA. This is in line with earlier studies. A Danish study of 1250 axSpA patients found that patients with nr-axSpA were more frequently women, HLA-B27 negative, had shorter time since diagnosis, higher VAS scores and BASDAI, but lower CRP and Bath Ankylosing Spondylitis Metrology Index than patients with AS.<sup>11</sup> A French observational study of 361 axSpA patients and a study from the German GESPIC cohort found the same differences in AS versus nr-axSpA regarding gender, disease duration and CRP.<sup>29 30</sup>

The strengths of this study are the generalizability of the results, which we consider to be high due to the inclusion of data from 12 registries across Europe, and a total of over

24 000 patients. A limitation is that selection bias based on data availability cannot be ruled out. Compliant subjects may be more likely to visit their doctor regularly and may therefore have more complete registry data, which could potentially lead to overestimation of drug retention rates. However, data have been collected prospectively and independently of the current research study.

Collaboration across registries may provide knowledge regarding prescription patterns, which has an interest in its own, but may also allow for investigation of heterogeneity across countries. The differences in prescription patterns and access to treatment imply that the results of pooling of data across countries should be interpreted with caution.<sup>20</sup>

In conclusion, data from 24195 European patients with axSpA who received their first TNFi were pooled, and the



**Figure 2** Kaplan-Meier curves (top) showing drug retention rates up to 24 months for pooled data and per register. The table (bottom) shows the number of patients who were still being treated at the corresponding time points.

retention and response rates were reported. Approximately a third of patients were in ASDAS inactive disease state after 6 months, and 80% were still receiving the same TNFi after 1 year. The EuroSpA collaboration offers unprecedented opportunities for providing real-world evidence on the effectiveness of biological drugs in European patients with axSpA.

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**Acknowledgements** On behalf of the EuroSpA Scientific Committee, the authors acknowledge Novartis Pharma AG and IQVIA for supporting the EuroSpA collaboration.

**Contributors** Study leads were CHB, LMØ, MØ and MLH. All authors took part in discussions around setting up the collaboration and planning this study. The study analysis plan was drafted by CHB, LMØ, MØ and MLH and all authors gave input and approved it. Data cleaning was performed by NSK, LMØ, CHB and overseen by MØ and MLH. Data analyses were conducted by NSK, CHB and LMØ. The manuscript was drafted by CHB, MMØ and MLH and the final version of the manuscript was revised and approved by all authors, who also approved submission.

**Funding** The EuroSpA collaboration was financially supported by Novartis. Novartis had no influence on the data collection, statistical analyses, manuscript preparation or decision to submit.

**Competing interests** LMØ: Novartis; CHB: Novartis; JA: has entered into agreements with Abbvie, BMS, Lilly, Merck, Pfizer, Roche, Samsung Bioepis, and UCB, mainly for safety monitoring via the Swedish ARTIS system, and received a travel reimbursement from Novartis. Karolinska Institutet has received remuneration for JA's participation in meetings arranged by Pfizer and by Lilly; AC: AbbVie, Celgene, Eli Lilly, Janssen-Cilag, MSD, Novartis, Pfizer and UCB; HM: AbbVie, MSD, Novartis, Pfizer, Sanofi; FO: Abbvie, Novartis, Pfizer, Roche, UCB; EKK: none; DN: AbbVie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, Sandoz, UCB; MJS: Abbvie, Biogen, Roche, Lilly, Pfizer, Novartis; Catalin Codreanu: AbbVie, Amgen, Angellini, Astra Zeneca, BMS, Egis, MSD, Pfizer, Richter, Roche, Sanofi, Servier, Teva, UCB, Zentiva; JGR: none; ZR: speaker or consulting fees from Abbvie, Amgen, Biogen, CellGen, Eli-Lilly, Jansen, Medis, MSD, Novartis, Pfizer, and Roche. BioRx.si has received funding for clinical research paid to Društvo za razvoj revmatologije from AbbVie, Celgene, Celtrion, Eli Lilly, Johnson & Johnson, Medis, MSD, Novartis, Pfizer and Roche; BG: Amgen, Novartis, Pfizer; MJN: Abbvie, Lilly, Pfizer, Novartis; KP: AbbVie, Roche, Pfizer, Amgen, Sanofi, Egis, BMS, UCB, MSD, Eli Lilly; TKK: AbbVie, Biogen, BMS, Celltrion, Egis, Eli Lilly, MSD, Mylan, Novartis, Oktal, Orion Pharma, Hospira/Pfizer, Roche, Sandoz, Sanofi and UCB; AB: Abbvie, Lilly, MSD, Novartis, Pfizer; MT: Abbvie, Amgen, Biogen, CellGen, Eli-Lilly, Jansen, Medis, MSD, Novartis, Pfizer, and Roche; FI: BMS, Pfizer, Abbvie, UCB, Roche, Celgene, Eli-Lilly, Hospira, Janssen, Merck; LHH: Novartis; MØ: Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Hospira, Janssen, Merck, Novartis, Orion, Pfizer, Regeneron, Roche, UCB; MLH: Abbvie, Biogen, BMS, CellTrion, MSD, Novartis, Orion, Pfizer, Samsung, UCB.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request.

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