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Ornbjerg, Lykke M.

2022-10

Ornbjerg , L M , Linde , L , Georgiadis , S , Rasmussen , S H , Lindström , U , Askling , J , Michelsen , B , Di Giuseppe , D , Wallman , J K , Pavelka , K , Zavada , J , Nissen , M J , Jones , G T , Relas , H , Pirila , L , Rotar , Z , Geirsson , A J , Gudbjornsson , B , Kristianslund , E K , Horst-Bruinsma , I V S , Loft , A G , Laas , K , Iannone , F , Corrado , A , Ciurea , A , Santos , M J , Santos , H , Codreanu , C , Akkoc , N , Gunduz , O S , Glintborg , B , Ostergaard , M & Hetland , M L 2022 , ' Predictors of ASDAS-CRP inactive disease in axial spondyloarthritis during treatment with TNF-inhibitors : Data from the EuroSpA collaboration ' , Seminars in Arthritis and Rheumatism , vol. 56 , 152081 . https://doi.org/10.1016/j.semarthrit.2022.15

http://hdl.handle.net/10138/348150
https://doi.org/10.1016/j.semarthrit.2022.152081

Seminars in Arthritis and Rheumatism 56 (2022) 152081

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Predictors of ASDAS-CRP inactive disease in axial spondyloarthritis during treatment with TNF-inhibitors: Data from the EuroSpA collaboration

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https://doi.org/10.1016/j.semarthrit.2022.152081

Available online 10 August 2022

ARTICLE INFO

Keywords:
Axial spondyloarthritis
TNF-inhibitors
Predictors
Ankylosing spondylitis disease activity score

ABSTRACT

Objectives: In patients with axial spondyloarthritis (axSpA) initiating their first tumor necrosis factor alpha-inhibitor (TNFi), we aimed to identify common baseline predictors of Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) inactive disease (primary objective) and clinically important improvement (CII) at 6 months, and drug retention at 12-months across 15 European registries.

Methods: Baseline demographic and clinical characteristics were collected. Outcomes were investigated per registry and in pooled data using logistic regression analyses on multiply imputed data.

Results: The consistency of baseline predictors in individual registries justified pooling the data. In the pooled dataset (n = 21,196), the 6-month rates for ASDAS inactive disease and ASDAS CII were 26% and 51%, and the 12-month drug retention rate 65% in patients with available data (n = 9,845, n = 6,948 and n = 21,196, respectively). Nine common baseline predictors of ASDAS inactive disease, ASDAS CII and 12-month drug retention were identified, and the odds ratios (95%-confidence interval) for ASDAS inactive disease were: age, per year: 0.97 (0.97–0.98), men vs. women: 1.88 (1.60–2.22), current vs. non-smoking: 0.76 (0.63–0.91), HLA-B27 positive vs. negative: 1.51 (1.20–1.91), TNF start year 2015–2018 vs. 2009–2014: 1.24 (1.06–1.45), CRP>10 vs. ≤10 mg/l: 1.49 (1.25–1.77), one unit increase in health assessment questionnaire (HAQ): 0.77 (0.58–1.03), one-millimeter (mm) increase in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) fatigue and spinal pain: 0.99 (0.99–1.00) and 0.99 (0.99–1.99), respectively

Conclusion: Common baseline predictors of treatment response and adherence to TNFi could be identified across data from 15 European registries, indicating that they may be universal across different axSpA populations.

Introduction

Tumor necrosis factor inhibitors (TNFi) have contributed to major improvements in clinical outcomes and quality of life for patients with axial spondyloarthritis (axSpA), including both ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA). Nonetheless, many patients treated with TNFi fail to achieve a treatment target of remission or low disease activity [1–3]. As treatment options expand, it has become increasingly important to identify the patients likely to respond to a TNFi to guide treating clinicians in the decision-making process.

Randomized controlled trials (RCTs) and observational studies have reported Human Leukocyte Antigen subtypes B*2701–2759 (HLA-B27) positivity, high C-reactive protein (CRP), male sex, young age and short disease-duration as predictors for good treatment response to TNFi [4–9], as assessed by drug retention or patient-reported outcomes such as bath ankylosing spondylitis disease activity index (BASDAI) [10] and the assessment of spondyloarthritis international society (ASAS) response criteria [11]. The ankylosing spondylitis disease activity score (ASDAS), developed in 2009, has been suggested to reflect the inflammatory disease processes better than BASDAI, as it includes either the CRP or erythrocyte sedimentation rate (ESR) [12–14]. Despite this, only smaller studies have reported on predictors of ASDAS inactive disease, with inconsistent results [15–18]. The EuroSpA research collaboration network (RCN) has presented cross-country data on treatment response to TNFi in axSpA, demonstrating significant differences in baseline characteristics and treatment outcomes across European countries [3, 19]. These differences may contribute to the inconsistency in observed baseline predictors across single country studies, introducing uncertainty as to whether such predictors can be considered central to the disease processes in axSpA, or rather to reflect differences in population characteristics and treatment practices. The EuroSpA provides a unique opportunity to identify potential common predictors across individual countries and in a large pooled cohort, which has not previously been done.

Thus, the primary aim of this study was to identify baseline predictors of achieving ASDAS inactive disease after 6 months in axSpA patients starting a first TNFi. Secondary aims were to identify baseline predictors of ASDAS clinically important improvement (CII) after 6 months, as well as 12-month drug retention. All analyses were done per registry and in pooled cohorts (one for each outcome).

Methods

Data sources

The present study included secondary use of data on patients registered with an axSpA diagnosis from 15 European registries: ATTRA (Czech Republic), DANBIO (Denmark), ROB-FIN (Finland), ICEBIO (Iceland), GISEA (Italy), ARC (Netherlands), NOR-DMARD (Norway), Reuma.pt (Portugal), RRBR (Romania), biorx.si (Slovenia), BIO-BADASER (Spain), SRQ/ARTIS (Sweden), SCQM (Switzerland), TURK-BIO (Turkey) and BSRBR-AS (United Kingdom). In all registries, data are collected prospectively in patients receiving routine care. Based on a predefined study protocol, anonymized data were uploaded by individual registries onto a secured central server.

Patients

Patients were included if they had a registered diagnosis of axSpA (incl. AS and nr-axSpA), were aged ≥18 years at initial diagnosis, had initiated a first TNFi treatment after diagnosis and no later than 90 years of age, with a start date between January 1st 2009 and December 31st 2018.

Visits and covariates

The baseline visit was defined as a registered visit from 30 days before to 30 days after the registered date of TNFi treatment start (i.e. baseline date), with priority given to the closest visit before treatment start. The allowed 30-day window *after* the baseline date was chosen to accommodate that in some cases the decision to treat was followed by a short waiting period before the treatment was actually initiated. The 6-month visit was defined as the one closest in time to 180 days after the TNFi treatment start date (baseline date), within a range of 90 to 270 days. Baseline variables included demographics, clinical measures, TNFi agent and start year, and patient-reported outcomes, see Table 1. The ASDAS based on CRP at baseline and after 6 months was calculated in registries with the available single components [20].

Endpoints

The primary endpoint was ASDAS inactive disease (<1.3) at 6 months on the 1st TNFi. Secondary endpoints were ASDAS CII, i.e. a

Table 1
Baseline characteristics of axSpA patients pooled and stratified by registry for 1st TNFi treatment.

Country	All	Czech Republic	Denmark	Finland	Iceland	Italy	Netherlands	Norway	Portugal	Romania	Slovenia	Spain	Sweden	Switzerland	Turkey	UK
Registry	Pooled	ATTRA	DANBIO	ROB-FIN	ICEBIO	GISEA	ARC	NOR-DMARD	Reuma.pt	RRBR	Biorx.si	BIOBADASER	SRQ/ ARTIS	SCQM	TURKBIO	BSRBR-AS
Number of patients	$n = 21,196$	$n = 2002$	$n = 2877$	$n = 574$	$n = 241$	$n = 1212$	$n = 106$	$n = 1235$	$n = 1119$	$n = 606$	$n = 516$	$n = 562$	$n = 6033$	$n = 1294$	$n = 1726$	$n = 1093$
Demography, diagnosis and lifestyle																
Age at treatment start, years	41 (33–51)	40 (33–48)	40 (31–50)	39 (31–49)	42 (33–52)	47 (38–56)	48 (39–56)	40 (32–50)	42 (34–52)	43 (34–51)	47 (37–56)	45 (36–54)	41 (31–51)	42 (33–52)	38 (31–46)	44 (34–55)
Age at diagnosis, years	35 (27–44)	33 (26–40)	36 (28–45)	32 (25–40)	37 (28–45)	42 (33–52)	40 (32–49)	32 (26–40)	35 (27–44)	35 (27–44)	39 (31–48)	37 (29–46)	34 (27–44)	36 (28–46)	33 (26–41)	35 (27–44)
Time since diagnosis, years	2 (0–8)	5 (1–10)	1 (0–4)	4 (1–11)	1 (0–7)	1 (0–5)	5 (1–12)	2 (0–9)	4 (1–10)	3 (1–10)	4 (1–10)	2 (1–8)	1 (0–6)	1 (0–6)	3 (1–7)	4 (1–13)
Men, n (%)	12,459 (59%)	1404 (70%)	1682 (58%)	326 (57%)	152 (63%)	627 (52%)	62 (58%)	684 (55%)	571 (51%)	444 (73%)	316 (61%)	388 (69%)	3421 (57%)	650 (50%)	999 (58%)	733 (67%)
BMI, kg/m^2	25.8 (23.1–29.3)	26.1 (23.4–29.4)	25.4 (22.8–28.7)	25.6 (23.1–29.0)	25.1 (22.9–27.5)	25.2 (22.7–28.3)	24.4 (22.0–28.1)	NA	25.3 (22.8–28.7)	26.1 (23.4–29.5)	26.0 (23.5–29.0)	26.3 (23.7–29.6)	NA	25.2 (22.7–28.6)	26.3 (23.5–29.6)	27.1 (23.9–31.2)
Smoking status, current, n (%)	4284 (24%)	402 (27%)	981 (35%)	49 (20%)	26 (17%)	52 (9%)	NA	267 (24%)	227 (27%)	86 (14%)	125 (24%)	169 (32%)	599 (12%)	399 (34%)	663 (42%)	239 (27%)
Clinical measures																
HLA-B27 positive, n (%)	6913 (75%)	1792 (90%)	849 (71%)	293 (89%)	27 (96%)	85 (61%)	76 (75%)	800 (82%)	539 (61%)	324 (53%)	371 (81%)	394 (75%)	NA	724 (62%)	109 (60%)	530 (76%)
Peripheral arthritis*, n (%)	4385 (32%)	NA	560 (29%)	147 (34%)	21 (26%)	230 (26%)	43 (41%)	165 (15%)	384 (38%)	155 (26%)	183 (35%)	23 (27%)	1173 (33%)	635 (49%)	270 (25%)	396 (38%)
CRP, mg/l	8 (3–20)	19 (11–30)	6 (2–16)	6 (3–14)	8 (3–21)	NA	5 (2–15)	5 (2–10)	9 (3–24)	22 (16–44)	8 (2–19)	NA	6 (2–16)	5 (2–12)	12 (4–26)	6 (2–18)
ESR, mm/hr	17 (8–33)	30 (18–42)	NA	9 (5–23)	NA	17 (8–31)	16 (6–34)	12 (6–24)	24 (10–43)	42 (30–62)	21 (10–37)	18 (8–35)	13 (6–28)	12 (6–22)	NA	11 (5–23)
BASMI (mm)	3.0 (1.6–4.0)	NA	2.0 (1.0–4.0)	NA	3.0 (2.0–4.0)	3.0 (2.0–4.0)	2.4 (2.0–3.1)	NA	3.0 (2.0–5.0)	NA	NA	NA	3.0 (2.0–4.0)	2.5 (1.7–3.5)	3.0 (1.0–5.0)	4.0 (2.7–5.4)
Physician global score (mm)	41 (24–60)	65 (50–79)	27 (14–45)	39 (21–50)	62 (49–74)	50 (30–70)	NA	33 (24–45)	52 (40–70)	NA	60 (30–70)	NA	40 (25–50)	50 (40–60)	34 (17–60)	NA
ASDAS-CRP (units)	3.5 (2.8–4.1)	4.0 (3.5–4.6)	3.5 (2.9–4.1)	2.8 (2.1–3.6)	3.8 (3.2–4.4)	NA	3.4 (2.6–4.0)	3.0 (2.3–3.6)	3.6 (3.0–4.2)	4.7 (4.3–5.1)	3.8 (3.3–4.5)	NA	3.2 (2.5–3.8)	3.2 (2.6–3.8)	3.5 (2.9–4.0)	3.7 (3.1–4.3)
TNFi-treatment																
1st TNFi drug, n (%)																
Infliximab	4600 (22%)	371 (19%)	987 (34%)	107 (19%)	190 (79%)	233 (19%)	11 (10%)	179 (14%)	163 (15%)	113 (19%)	62 (12%)	71 (13%)	1529 (25%)	213 (16%)	368 (21%)	3 (0%)
Etanercept	5183 (24%)	363 (18%)	411 (14%)	160 (28%)	21 (9%)	289 (24%)	42 (40%)	352 (29%)	304 (27%)	150 (25%)	99 (19%)	158 (28%)	1837 (30%)	245 (19%)	418 (24%)	334 (31%)
Adalimumab	6891 (33%)	821 (41%)	742 (26%)	194 (34%)	2 (1%)	525 (43%)	53 (50%)	234 (19%)	376 (34%)	215 (35%)	227 (44%)	192 (34%)	1709 (28%)	426 (33%)	517 (30%)	658 (60%)
Certolizumab	1242 (6%)	70 (3%)	226 (8%)	19 (3%)	0 (0%)	18 (1%)	0 (0%)	290 (23%)	29 (3%)	1 (0%)	12 (2%)	40 (7%)	256 (4%)	38 (3%)	161 (9%)	82 (8%)
Golimumab	3280 (15%)	377 (19%)	511 (18%)	94 (16%)	28 (12%)	147 (12%)	0 (0%)	180 (15%)	247 (22%)	127 (21%)	116 (22%)	101 (18%)	702 (12%)	372 (29%)	262 (15%)	16 (1%)

(*continued on next page*)

Table 1 (*continued*)

Country	All	Czech Republic	Denmark	Finland	Iceland	Italy	Netherlands	Norway	Portugal	Romania	Slovenia	Spain	Sweden	Switzerland	Turkey	UK
Registry	Pooled	ATTRA	DANBIO	ROB-FIN	ICEBIO	GISEA	ARC	NOR-DMARD	Reuma.pt	RRBR	Biorx.si	BIOBADASER	SRQ/ ARTIS	SCQM	TURKBIO	BSRBR-AS
1st TNFi start year**, n (%)																
2009–2014	11,237 (53%)	1143 (57%)	1628 (57%)	408 (71%)	111 (46%)	982 (81%)	106 (100%)	809 (66%)	544 (49%)	0 (0%)	350 (68%)	139 (25%)	3198 (53%)	877 (68%)	615 (36%)	327 (30%)
2015–2018	9959 (47%)	859 (43%)	1249 (43%)	166 (29%)	130 (54%)	230 (19%)	0 (0%)	426 (34%)	575 (51%)	606 (100%)	166 (32%)	423 (75%)	2835 (47%)	417 (32%)	1111 (64%)	766 (70%)
Patient reported outcomes																
Pain score (mm)	65 (45–79)	70 (50–80)	66 (50–80)	53 (29–72)	71 (50–79)	60 (45–80)	NA	49 (30–67)	NA	NA (NA-NA)	70 (60–80)	NA	61 (41–75)	70 (50–80)	73 (52–80)	70 (50–80)
Fatigue score (mm)	68 (46–80)	NA	72 (54–85)	NA	74 (48–86)	NA	NA	50 (20–70)	NA	80 (80–90)	NA	NA	64 (41–78)	60 (50–80)	70 (50–75)	80 (60–90)
Patient global score (mm)	66 (48–80)	70 (50–80)	73 (57–86)	50 (23–69)	75 (59–85)	60 (50–80)	60 (30–80)	54 (34–71)	70 (50–80)	80 (80–90)	70 (60–80)	60 (50–70)	59 (40–74)	70 (50–80)	70 (51–78)	75 (60–90)
HAQ (units)	0.8 (0.5–1.2)	1.1 (0.8–1.5)	0.8 (0.5–1.2)	0.6 (0.2–1.0)	0.9 (0.5–1.4)	0.9 (0.4–1.5)	NA	0.5 (0.2–0.8)	NA	1.9 (1.5–2.1)	1.0 (0.5–1.4)	NA	0.8 (0.4–1.1)	NA	0.8 (0.5–1.1)	NA
BASDAI (mm)	58 (42–72)	65 (53–76)	61 (48–73)	42 (24–58)	64 (45–78)	50 (35–67)	47 (32–61)	48 (32–64)	62 (48–75)	74 (66–82)	69 (57–80)	56 (45–70)	56 (40–69)	56 (41–69)	43 (31–59)	67 (52–79)
BASDAI Q1 fatigue (mm)	66 (48–80)	70 (55–80)	70 (52–83)	49 (21–70)	66 (50–84)	NA	70 (35–85)	59 (34–75)	70 (50–80)	80 (80–90)	80 (60–80)	NA	63 (44–77)	60 (50–80)	50 (28–65)	80 (60–90)
BASDAI Q2 pain spinal (mm)	70 (51–82)	74 (60–85)	74 (59–87)	57 (28–74)	72 (64–90)	NA	70 (60–90)	58 (36–76)	76 (60–89)	90 (80–100)	80 (70–90)	NA	65 (45–80)	70 (50–80)	63 (50–71)	80 (60–90)
BASDAI Q3 pain joints (mm)	50 (20–70)	60 (38–78)	49 (19–73)	20 (3–47)	65 (17–80)	NA	40 (10–70)	28 (7–57)	54 (20–80)	60 (20–80)	60 (40–80)	NA	47 (15–70)	50 (20–70)	44 (20–60)	60 (30–80)
BASDAI Q4 tender joints (mm)	55 (30–75)	60 (45–77)	58 (31–76)	30 (7–58)	50 (10–80)	NA	40 (8–60)	42 (17–66)	68 (43–80)	70 (50–90)	70 (50–80)	NA	52 (27–73)	50 (30–75)	30 (7–60)	60 (30–80)
BASDAI Q5 stiffness severity (mm)	69 (45–83)	73 (58–87)	71 (51–88)	49 (22–70)	84 (58–92)	NA	40 (20–70)	59 (34–77)	71 (50–88)	90 (80–100)	80 (60–90)	NA	65 (41–81)	70 (40–80)	30 (20–54)	80 (60–90)
BASDAI Q6 stiffness duration (mm)	51 (30–80)	66 (45–86)	55 (36–84)	48 (20–76)	76 (50–94)	NA	50 (20–80)	50 (27–76)	50 (25–79)	90 (70–100)	60 (40–90)	NA	50 (25–75)	40 (20–70)	41 (21–60)	80 (42–100)
BASFI (mm)	46 (26–66)	54 (37–70)	49 (30–66)	28 (12–48)	47 (25–63)	40 (20–60)	47 (28–72)	NA	60 (39–76)	NA	59 (43–74)	NA	38 (20–59)	35 (16–55)	26 (16–43)	66 (44–82)

Data are as observed, median (IQR) or percentage. Percentages are calculated based on the number of patients with available data.

* Peripheral arthritis was defined as either ≥1 swollen joint in either 28 or 66 joint counts at baseline or "yes" in the question regarding arthritis in the ASAS criteria.

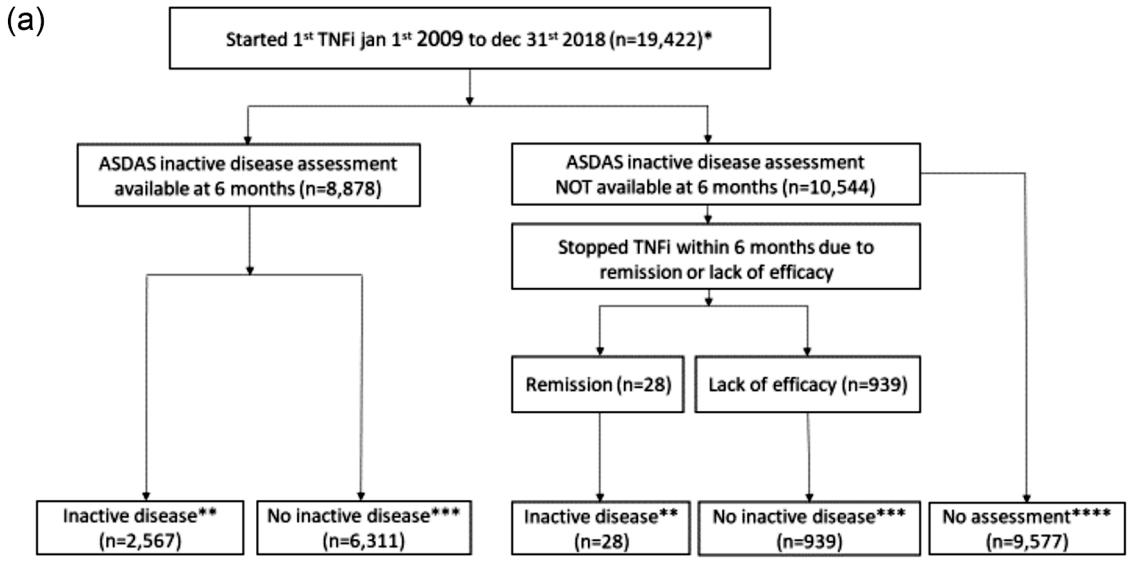
** 2009 was chosen as the first three bDMARDs (adalimumab, etanercept and infliximab) were then well-established treatment options across the European countries. 2015 was chosen as secukinumab was approved as the first non-TNFi bDMARD treatment option that year. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; Q1-Q6: question 1–6; BASFI: Bath Ankylosing Spondylitis Function Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: Body Mass Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HLA-B27: Human Leukocyte Antigen subtypes B*2701–2759; IQR: Interquartile Range; TNFi: Tumour Necrosis Factor alpha inhibitor.

reduction ≥1.1 from baseline to 6 months, and 12-month drug retention on the 1st TNFi [14]. Registries without CRP and/or individual BASDAI components were excluded from analyses of ASDAS inactive disease and ASDAS CII.

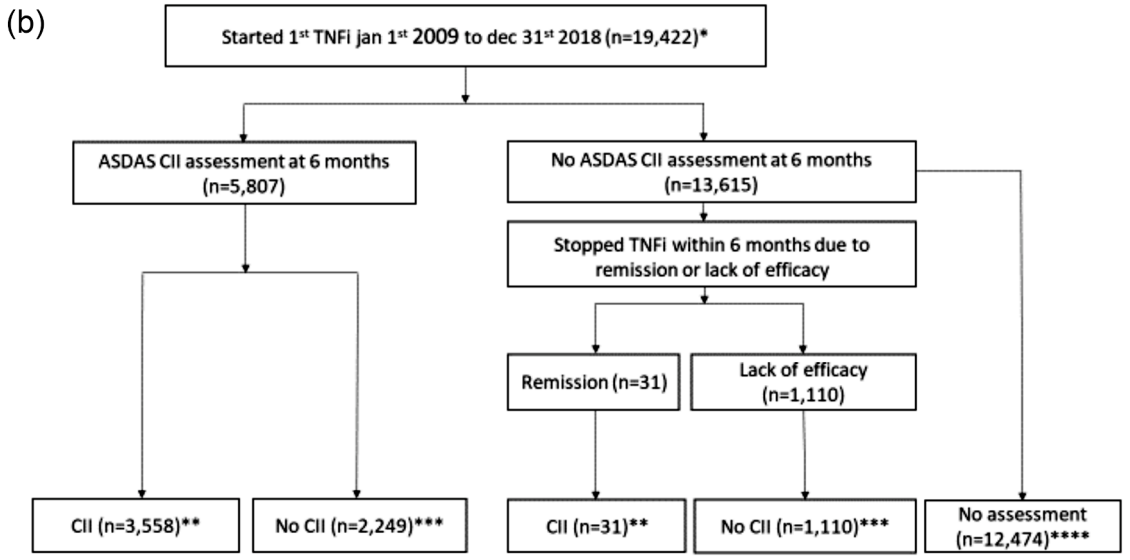
Patients with unavailable 6-month ASDAS were classified as having achieved either ASDAS inactive disease or ASDAS CII based on the following arguments: 1. They had stopped the treatment within 6 months from treatment start *and* no subsequent treatment was started within the 6 months, and 2. The clinician had chosen "remission" as the discontinuation reason from a number of prespecified options, see Fig. 1a and b. Patients who stopped treatment during the first 6 months due to lack of effect according to the opinion of the clinician were considered *not* achieving ASDAS inactive disease or ASDAS CII. Patients discontinuing treatment due to AE or other reasons were not included in the analyses. The additional classification was applied to reduce bias from basing prediction models only on patients continuing treatment for 6 months or more.

Drug retention

The treatment duration was defined as the number of days between the registered date of treatment start and the registered stop date. Switch to a biosimilar of the same drug was disregarded. Treatment duration was censored by the date of data extraction, date of death, or end of registry follow-up, whichever came first. Further details on drug retention assumptions are presented in the supplementary data S1.



TNFi: Tumour Necrosis Factor alpha inhibitor; ASDAS: Ankylosing Spondylitis Disease Activity Score.
*Excluding Italy and Spain due to no available CRP and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) components; **inactive disease: n=2,595; ***no inactive disease: n=7,250; n=9,845 *with* available data; n=9,577 *without* available data; ****including patients stopping TNFi *after* 6 months for all reasons, patients stopping TNFi *within* 6 months due to adverse events and other reasons and patients continuing on TNFi but without an assessment.



TNFi: Tumour Necrosis Factor alpha inhibitor; ASDAS CII: Ankylosing Spondylitis Disease Activity Score Clinically Imortant Improvement.
*Excluding Italy and Spain due to no available CRP and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) components; **CII: n=3,589; ***no CII: n=3,359; n=6,948 *with* available data; n=12,474 *without* available data; ****including patients stopping TNFi *after* 6 months for all reasons, patients stopping TNFi *within* 6 months for AE or other reasons and patients continuing on TNFi but without an assessment.

Fig. 1. a. Flowchart for patients starting 1st TNF-inhibitor (ASDAS-inactive disease). Fig. 1b. Flowchart for patients starting 1st TNF-inhibitor (ASDAS-clinically important improvement).

Ethics

All participating registries obtained necessary approvals from relevant authorities prior to data transfer to the EuroSpA coordinating center [3]. This study was designed, implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [21] and the ethical principles laid down in the Declaration of Helsinki.

Statistics

Descriptive analyses of baseline patient characteristics per registry and in the pooled cohort were conducted. In the pooled cohort, baseline characteristics for patients with and without available data on ASDAS inactive disease and ASDAS CII at follow-up were also described.

Logistic regression analyses

Logistic regression analyses were used to identify baseline variables associated with the primary and secondary endpoints. Regression models were applied separately per registry and in the pooled cohort. Before applying logistic regression analyses, we assessed the frequency and proportion of patients achieving the outcome and events-per-variable (EPV = number of events/degrees of freedom to represent all independent variables) considering all and available independent variables. An event was defined as the less frequent outcome (i.e. achieving a response measure or not) in logistic regression analyses. Likelihood ratio tests were used to assess all models. Results of the multivariate models are given as odds ratio (OR) and confidence interval (CI). The following sections describe details of the regression analyses.

a *Independent variables*

Sex, smoking status (current vs. previous/never), HLA-B27 status (positive vs. negative), peripheral arthritis (yes vs. no), year of TNFi start (2009–2014 vs. 2015–2018), and CRP ($\leq$10 vs. >10 mg/l) were included as categorical independent variables. Peripheral arthritis was defined as either $\geq$1 swollen joint in either 28 or 66 joint counts at baseline or "yes" in the question regarding arthritis in the ASAS criteria. TNFi initiation since January 1st 2009 was chosen as the start of data collection, as the first three bDMARDs (adalimumab, etanercept and infliximab) were then well-established treatment options across the European countries. 2015 was chosen as the separator between the time periods, as secukinumab was approved as the first non-TNFi bDMARD treatment option that year. The CRP cut-off was decided based on the various detection limits used across registries. Age at treatment start, time since diagnosis, body mass index (BMI), bath ankylosing spondylitis metrology index (BASMI), bath ankylosing spondylitis functional index (BASFI) [22], each bath ankylosing spondylitis disease activity index (BASDAI) component, patient and physician global scores, and health assessment questionnaire (HAQ) [23] were included as continuous variables. Age at diagnosis, ESR and patient pain and fatigue were excluded from the models as they were thought to represent an overlap with time since diagnosis, CRP and BASDAI pain and fatigue components, respectively.

a *Missing values*

Multiple imputation by chained equations (MICE) was used to impute all baseline independent variables in a pooled dataset containing all registries regardless of the extent of missingness. The number of imputed datasets was defined based on the missingness of values in the considered data (40 imputed datasets). Registry-specific datasets were subsequently extracted from the multiple imputed overall data.

a *Variable selection*

For each endpoint, the selection was performed separately in each of the 40 imputed datasets [24]. Initially, univariate logistic regression analyses were performed for all independent variables. Variables with a p-value <0.20 in univariate analyses were included in the initial multivariate model, where a backward stepwise selection was applied. Next, independent variables excluded in univariate analyses were introduced one at a time in the multivariate model and their significance tested. The final model included the predictors that appeared in at least half of the 40 separate models. Once the set of predictors was selected, the model was fitted to all 40 imputed datasets and the model estimates were pooled according to Rubin's rules [25]. The fit of the final model was assessed by a pseudo R^2 index [26].

Analyses in individual registries

To compare the selected predictors across registries, prediction models were first applied in each registry. Dichotomous variables, where only one category was available in the registry and variables not delivered by the registry were excluded from the list of possible predictors.

In the summary of predictors per registry, results for registries with EPV$\geq$1 (per available independent variables) are shown, while final multivariate models are only presented for registries with EPV$\geq$10 (per available independent variables). A significance level of 0.157 was chosen due to small EPV values in some registries, corresponding to a 85% CI [27]. The consistency of regression analyses per registry was assessed to determine if pooling the data was feasible.

Analyses in pooled cohort

For each outcome, the pooled dataset was split into a derivation cohort and a validation cohort, ensuring that 50% of patients from each registry go into each cohort, respectively. Registries with EPV<1 in the derivation cohort, considering conservatively all independent variables, were eventually excluded from the pooled data. Age, sex and registry were a priori forced into the prediction models. The assumption of linearity of continuous variables was additionally explored and non-linear continuous predictors were categorized based on quartiles. A significance level of 0.05 and a corresponding 95% CI was applied. The performance of the final multivariate models was assessed via external validation by calculating the area under the receiver operating curve (AUROC) in the validation cohort [28].

Additional analyses

To assess whether differences in per registry rates of ASDAS inactive disease, ASDAS CII and drug retention impacted the selected predictors, the pooled cohort was stratified into three levels based on the frequency of the observed outcomes, and prediction models were applied to each stratum, adjusting for registry. The variable selection process was similar to the analyses in individual registries.

R version 4.1.0 was used for statistical analyses.

Results

Cohorts

Overall, 21,196 axSpA patients started their 1st TNFi treatment between January 1st, 2009 and December 31st, 2018 and were included. Baseline patient characteristics by registry and pooled are shown in Table 1 and corresponding information on available data in supplementary table S2. Patients without 6-month follow-up data tended to have lower baseline patient global scores, while the remaining baseline characteristics were largely similar, see supplementary table S3.

Table 2
Summary of predictors per registry* for ASDAS inactive disease after 6 months of treatment with 1st TNFi.

Country	Czech Republic	Denmark	Finland	Iceland	Netherlands	Norway	Portugal	Romania	Slovenia	Sweden	Switzerland	Turkey	UK	Row sum**
Registry	ATTRA	DANBIO	ROB-FIN	ICEBIO	ARC	NOR-DMARD	Reuma.pt	RRBR	Biorx.si	SRQ/ ARTIS	SCQM	TURKBIO	BSRBR-AS	
Number of patients	1255	1805	143	117	51	906	785	567	129	2423	366	869	429	
N (%) with ASDAS inactive disease	371 (30%)	382 (21%)	69 (48%)	43 (37%)	11 (22%)	309 (34%)	192 (24%)	139 (25%)	21 (16%)	670 (28%)	59 (16%)	282 (32%)	47 (11%)	
EPV	20.6	19.1	3.6	2.1	0.7	18.2	10.1	8.7	1.1	37.2	3.1	14.1	2.6	
Age at treatment start, years	–	–	–			–	–	–		–	–	–	–	10
Men	+	+		+		+	+		+	+	+	+	+	10
Time since diagnosis, years		+							–					2
BMI, kg/m^2	–	–	–			NA	–	–		NA	–	–	–	8
Smoking status, current	–				NA				–	–	–	–		5
HLA-B27 positive	+	+				+				NA	+	+	+	6
Peripheral arthritis***	NA									+				1
1st TNFi start, year (2015–2018)****	+	+			const	+		const	–		+	+		6
CRP>10 mg/l		+				+				+	+			4
Patient global score, mm											–			1
Physician global score, mm	–				NA			NA		–		–	NA	3
HAQ, units	–				NA	–	NA	–	–		NA		NA	4
BASDAI Q1 fatigue, mm		–	–			–	–	–		–	–		–	8
BASDAI Q2 pain spinal, mm	–	–		–				–		–				5
BASDAI Q3 pain joints, mm						–	+						+	3
BASDAI Q4 tender joints, mm	+											+		2
BASDAI Q5 stiffness severity, mm	+						–		–	+				4
BASDAI Q6 stiffness duration, mm		–				–								2
BASFI, mm	–	–		–		NA	–	NA		–		–	–	7
BASMI, mm	NA	–	NA			NA	–	NA	NA	–	–	–		5
Sum of independent predictors*****	12	12	3	3	–	9	8	5	6	11	10	10	7	
Total number of available IVs******	18	20	19	20	16	17	19	16	19	18	19	20	18	

Baseline variables selected as predictors in at least half of the registries in which the variable is available are highlighted in bold.

* Italy and Spain excluded due to no available CRP and BASDAI components.

** number of registries in which a variable is selected as a predictor.

*** peripheral arthritis was defined as either ≥1 swollen joint in either 28 or 66 joint counts at baseline or "yes" in the question regarding arthritis in the ASAS criteria.

**** 2009 was chosen as the first three bDMARDs (adalimumab, etanercept and infliximab) were then well-established treatment options across the European countries. 2015 was chosen as secukinumab was approved as the first non-TNFi bDMARD treatment option that year.

***** sum of predictors selected per cohort.

****** number of independent variables (after excluding missing and constant variables). EPV: Events-per-variable per available independent variables (IVs), only results for registries with EPV>1are shown; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; Q1-Q6: question 1–6; BASFI: Bath Ankylosing Spondylitis Function Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: Body Mass Index; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; HLA-B27: Human Leukocyte Antigen subtypes B*2701–2759; TNFi: Tumour Necrosis Factor alpha inhibitor; OR: odds ratio; +: OR>1; -: OR<1; const: dichotomous variable, where only one category was available in the registry; NA: variable not delivered by the registry.

Table 3
Summary of predictors per registry* for ASDAS clinically important improvement after 6 months of treatment with 1st TNFi.

Country	Czech Republic	Denmark	Finland	Iceland	Netherlands	Norway	Portugal	Romania	Slovenia	Sweden	Switzerland	Turkey	UK	Row sum**
Registry	ATTRA	DANBIO	ROB-FIN	ICEBIO	ARC	NOR-DMARD	Reuma.pt	RRBR	Biorx.si	SRQ/ ARTIS	SCQM	TURKBIO	BSRBR-AS	
Number of patients	1173	1424	85	45	38	793	542	182	118	1379	275	663	231	
N (%) with ASDAS CII	935 (80%)	627 (44%)	35 (41%)	23 (51%)	16 (42%)	360 (45%)	293 (54%)	143 (79%)	55 (47%)	533 (39%)	64 (23%)	427 (64%)	78 (34%)	
EPV	15.9	31.4	1.8	1.2	1	21.2	14.7	2.8	2.9	29.6	3.4	12.9	4.3	
Age at treatment start, years	–	–				–	–			–				5
Men	+	+			+	+	+			+	+	+		8
Time since diagnosis, years										+				1
BMI, kg/m^2	–	–	–		–	NA	–			NA	–	–		7
Smoking status, current		–			NA					–				2
HLA-B27 positive	+	+		const		+	+	+		NA	+	+	+	8
Peripheral arthritis***	NA				+				+					2
1st TNFi start (2015–2018)****	+	+		–	const			const				+		4
CRP>10 mg/l	+	+	+			+	+		+	+	+	+	+	10
Patient global score, mm		+				+	+	+	+	+		+		7
Physician global score, mm					NA			NA					NA	0
HAQ, units	–	–			NA	–	NA				NA	–	NA	4
BASDAI Q1 fatigue, mm		–								–				2
BASDAI Q2 pain spinal, mm	+	+				+					+	+		5
BASDAI Q3 pain joints, mm	+						+					+		3
BASDAI Q4 tender joints, mm							+					+	+	3
BASDAI Q5 stiffness severity, mm		+	+						–					3
BASDAI Q6 stiffness duration, mm	+	+								+				3
BASFI, mm		–	–			NA	–	NA		–		–	–	6
BASMI, mm	NA		NA			NA		NA	NA					0
Sum of independent predictors*****	10	14	4	1	3	7	9	2	4	9	5	11	4	
Total number of available IVs******	18	20	19	19	16	17	19	16	19	18	19	20	18	

Baseline variables selected as predictors in at least half of the registries in which the variable is available are highlighted in bold.

* Italy and Spain excluded due to no available CRP and BASDAI components.

** number of registries in which a variable is selected as a predictor.

*** peripheral arthritis was defined as either ≥1 swollen joint in either 28 or 66 joint counts at baseline or "yes" in the question regarding arthritis in the ASAS criteria.

**** 2009 was chosen as the first three bDMARDs (adalimumab, etanercept and infliximab) were then well-established treatment options across the European countries. 2015 was chosen as secukinumab was approved as the first non-TNFi bDMARD treatment option that year.

***** sum of predictors selected per cohort.

****** number of independent variables (after excluding missing and constant variables). EPV: Events-per-variable per available independent variables (IVs), only results for registries with EPV>1are shown; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; Q1-Q6: question 1–6; BASFI: Bath Ankylosing Spondylitis Function Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: Body Mass Index; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; HLA-B27: Human Leukocyte Antigen subtypes B*2701–2759; TNFi: Tumor Necrosis Factor alpha inhibitor; OR: odds ratio; +: OR>1; -: OR<1; const: dichotomous variable, where only one category was available in the registry; NA: variable not delivered by the registry.

Table 4
Summary of predictors per registry for 12-month drug retention on 1st TNFi.

Country	Czech Republic	Denmark	Finland	Iceland	Italy	Netherlands	Norway	Portugal	Romania	Slovenia	Spain	Sweden	Switzerland	Turkey	UK	Row sum*
Registry	ATTRA	DANBIO	ROB-FIN	ICEBIO	GISEA	ARC	NOR-DMARD	Reuma. pt	RRBR	Biorx.si	BIOBADASER	SRQ/ ARTIS	SCQM	TURKBIO	BSRBR-AS	
Number of patients	2002	2877	574	241	1212	106	1235	1119	606	516	562	6033	1294	1726	1093	
N (%) with 12-month drug retention	1468 (73)	1714 (60)	382 (67)	146 (60)	722 (60)	72 (68)	677(55)	814 (73)	449 (74)	348 (67)	353 (63)	4127 (68)	783(61)	119,469)	558 (51)	
EPV	29.7	58.1	10.1	4.8	37.7	2.1	32.8	16.1	9.8	8.8	23.2	105.9	26.9	26.6	29.7	
Age at treatment start, years	–	–										–		+		4
Men	+	+					+	+	+	+	+	+	+	+	+	11
Time since diagnosis, years	+					+										2
BMI, kg/m^2						–	NA				+	NA				2
Smoking status, current		–			–	NA			–	–		–	–			6
HLA-B27 positive	+	+			+		+	+	+		+	NA	+	+	+	10
Peripheral arthritis**	NA											–				1
1st TNFi start (2015–2018)* **	–	–		–		const	–	–	const	–	–		–	–	–	10
CRP>10 mg/l	+	+	+	+	NA		+	+		+	NA	+	+	+	+	11
Patient global score, mm											–					1
Physician global score, mm		+				NA			NA		NA	+			NA	2
HAQ, units	–	–			–	NA		NA			NA		NA		NA	3
BASDAI Q1 fatigue, mm	–	–			NA		–				NA	–				4
BASDAI Q2 pain spinal, mm		–	–		NA				–		NA	–		–	–	6
BASDAI Q3 pain joints, mm		–			NA						NA	–				2
BASDAI Q4 tender joints, mm					NA						NA					0
BASDAI Q5 stiffness severity, mm					NA					–	NA	+				2
BASDAI Q6 stiffness duration, mm					NA					–	NA					1
BASFI, mm							NA	–	NA		NA	–		–		3
BASMI, mm	NA	+	NA		+	+	NA		NA	NA	NA	+		+		5
Sum of independent predictors****	8	12	2	2	4	3	5	5	4	6	5	12	5	8	5	
Total number of available IVs*****	18	20	19	20	13	16	17	19	16	19	9	18	19	20	18	

Baseline variables that are selected as predictors in at least half of registries in which the variable is available are highlighted in bold.

* number of registries in which a variable is selected as a predictor.

** peripheral arthritis was defined as either ≥1 swollen joint in either 28 or 66 joint counts at baseline or "yes" in the question regarding arthritis in the ASAS criteria.

*** 2009 was chosen as the first three bDMARDs (adalimumab, etanercept and infliximab) were then well-established treatment options across the European countries. 2015 was chosen as secukinumab was approved as the first non-TNFi bDMARD treatment option that year.

**** sum of predictors selected per cohort.

***** number of independent variables (after excluding missing and constant variables). EPV: Events-per-variable per available independent variables (IVs), only results for registries with EPV>1are shown; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; Q1-Q6: question 1–6; BASFI: Bath Ankylosing Spondylitis Function Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: Body Mass Index; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; HLA-B27: Human Leukocyte Antigen subtypes B*2701–2759; TNFi: Tumour Necrosis Factor alpha Inhibitor; OR: odds ratio; +: OR>1; -: OR<1; const: dichotomous variable, where only one category was available in the registry; NA: variable not delivered by the registry.

ASDAS inactive disease and clinically important improvement

Of the 15 registries included in this study, 13 collected data on ASDAS based on CRP ($n = 19,422$). Among these, 8878 patients (46%) had an ASDAS assessment at the 6-month follow-up visit during the 1st TNFi treatment. A total of 967 patients stopped the treatment due to either remission or lack of efficacy within the first 6 months and were classified based on the discontinuation reason, resulting in 9845 (51%) available for analyses, see Fig. 1a. In total, 2595 of 9845 patients (26%) had achieved inactive disease at 6 months. Rates for inactive disease ranged from 11% to 48% across registries, Table 2. Corresponding results for ASDAS CII are presented in Fig. 1b and Table 3.

Drug retention

All patients initiating a 1st TNFi were included in the drug retention analyses. Of these, 13,807 (65%) were still on treatment at 12 months ranging from 51% to 74% across registries, Table 4.

Prediction analyses in individual registries

Twelve registries fulfilled the EPV criteria and were eligible for prediction analyses of the primary endpoint ASDAS inactive disease. Higher age at treatment start was selected as a negative predictor in 10 registries and male sex as a positive predictor in 10 registries. Higher BMI and BASDAI fatigue scores were negative predictors in 8 registries, while a higher BASFI score was a negative predictor in 7 registries, and the presence of HLA-B27 a positive predictor in 6 registries. TNF start year 2015–2018 was a positive predictor in 5 registries and a negative in 1 registry, while BASMI was a positive predictor in 5 registries. The remaining baseline variables were selected in less than half of the registries in which the variable was available, see Table 2 and supplementary table S4 for presentation of ORs.

Thirteen and 15 registries were eligible for analyses of the secondary endpoints ASDAS CII and 12-month drug retention, respectively. CRP >10 mg/l, male sex and HLA-B27 positivity were selected as positive predictors in more than half of the registries in which the variable was available for both endpoints. Higher patient global score was selected as a positive predictor in 7 and higher BMI and BASFI anegative predictor of ASDAS CII in 7 and 5 registries, respectively. TNFi start year 2015–2018 was selected as a negative predictor of 12-month drug retention in 10 registries and BASMI a positive predictor in 5 registries. The remaining baseline variables were selected in less than half of the registries in which the variable was available, see Tables 3-4 and supplementary tables S5-S6 for ORs.

Prediction analyses in the pooled cohort

The consistency of regression analyses per registry justified pooling the data. Nine common baseline predictors of ASDAS inactive disease, CII and 12-month drug retention were identified: male sex, positive HLA-B27 and CRP >10 mg/l were positive predictors, higher age at

Table 5
Univariate and final multivariate analyses for predicting ASDAS inactive disease, ASDAS clinically important improvement (CII) at 6 months and 12-month drug retention on 1st TNFi in pooled data (derivation cohorts).

	Analysis of ASDAS inactive disease (n = 4616)		Analysis of ASDAS CII (n = 3340)		Analysis of 12-month drug retention (n = 10,545)	
Number (%) achieving the outcome	1282(28%)		1707 (51%)		6828 (65%)	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
	OR (95%CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age at treatment start, years	0.96 (0.96 - 0.97)	0.98 (0.97 - 0.99)	0.98 (0.97 - 0.98)	0.98 (0.97 - 0.99)	0.99 (0.99 - 1.00)	0.99 (0.99 - 1.00)
Men	1.97 (1.71 - 2.26)	1.79 (1.51 - 2.12)	1.83 (1.59 - 2.10)	1.50 (1.26 - 1.79)	1.68 (1.55 - 1.83)	1.40 (1.28 - 1.54)
Time since diagnosis, years	0.99 (0.98 - 1.00)		1.01 (1.00 - 1.02)		1.00 (1.00 - 1.01)	
BMI, kg/m^2	0.91 (0.89 - 0.93)	0.93 (0.91 - 0.95)	0.94 (0.92 - 0.96)	0.93 (0.91 - 0.96)	0.99 (0.98 - 1.00)	
Smoking status, current	0.83 (0.71 - 0.97)	0.72 (0.59 - 0.87)	1.15 (0.98 - 1.35)	0.78 (0.64 - 0.95)	0.85 (0.77 - 0.94)	0.82 (0.74 - 0.92)
HLA-B27 positive	2.07 (1.66 - 2.59)	1.65 (1.27 - 2.15)	2.22 (1.78 - 2.78)	1.91 (1.46 - 2.51)	1.66 (1.47 - 1.88)	1.50 (1.31 - 1.72)
Peripheral arthritis*	0.92 (0.78 - 1.08)		1.17 (1.00 - 1.38)		0.97 (0.87 - 1.07)	
1st TNFi start (2015–2018)**	1.19 (1.04 - 1.36)	1.24 (1.06 - 1.45)	1.16 (1.01 - 1.33)	1.19 (1.00 - 1.41)	0.65 (0.60 - 0.70)	0.61 (0.55 - 0.66)
CRP>10 mg/l	1.16 (1.01 - 1.33)	1.36 (1.14 - 1.62)	4.82 (4.13 - 5.63)	4.03 (3.36 - 4.85)	1.49 (1.35 - 1.64)	1.31 (1.17 - 1.47)
Patient global score, mm	0.98 (0.98 - 0.98)		1.01 (1.01 - 1.02)	1.02 (1.01 - 1.02)	(0.99 - 1.00)	
Physician global score, mm	0.99 (0.99 - 0.99)		1.01 (1.01 - 1.01)		1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
HAQ, units	0.38 (0.33 - 0.44)	0.77 (0.58 - 1.03)	1.11 (0.97 - 1.26)	0.67 (0.51 - 0.89)	0.81 (0.75 - 0.88)	0.84 (0.75 - 0.93)
BASDAI Q1 fatigue, mm	0.98 (0.97 - 0.98)	0.99 (0.99 - 0.99)	1.00 (1.00 - 1.00)	0.99 (0.99 - 1.00)	0.99 (0.99 - 0.99)	0.99 (0.99 - 1.00)
BASDAI Q2 pain spinal, mm	0.98 (0.97 - 0.98)	0.99 (0.99 - 1.00)	1.01 (1.01 - 1.01)	1.01 (1.01 - 1.02)	0.99 (0.99 - 0.99)	0.99 (0.99 - 1.00)
BASDAI Q3 pain joints, mm	0.99 (0.99 - 0.99)		1.01 (1.00 - 1.01)	1.01 (1.01 - 1.01)	1.00 (0.99 - 1.00)	
BASDAI Q4 tender joints, mm	0.99 (0.98 - 0.99)		1.01 (1.00 - 1.01)		0.99 (0.99 - 1.00)	
BASDAI Q5 stiffness severity, mm	0.98 (0.98 - 0.99)		1.01 (1.00 - 1.01)		0.99 (0.99 - 1.00)	
BASDAI Q6 stiffness duration, mm	0.99 (0.99 - 0.99)		1.01 (1.00 - 1.01)	1.01 (1.00 - 1.01)	1.00 (0.99 - 1.00)	
BASFI, mm	0.97 (0.97 - 0.97)	0.99 (0.98 - 0.99)	1.00 (1.00 - 1.00)	0.99 (0.98 - 1.00)	0.99 (0.99 - 1.00)	
BASMI, mm	0.82 (0.77 - 0.87)	0.91 (0.84 - 0.98)	1.01 (0.97 - 1.06)		1.03 (0.99 - 1.06)	1.05 (1.00 - 1.10)
Time since diagnosis (2–5 years)				1.07 (0.85 - 1.35)		
Time since diagnosis (6–56 years)				1.54 (1.22 - 1.94)		
Pseudo R^2 **** (95% CI)		0.31 (0.27 - 0.34)		0.41 (0.37 - 0.45)		0.12 (0.10 - 0.14)
AUROC (95% CI)		0.76 (0.74 - 0.78)		0.80 (0.78 - 0.81)		0.66 (0.65 - 0.67)

Baseline variables that are common predictors across all outcomes are highlighted in bold. Registries with events per variable <1 were excluded from analyses: ARC excluded from all analyses, ICEBIO excluded from ASDAS CII analyses and Biorx.si excluded from ASDAS inactive disease analyses. Italy and Spain excluded from ASDAS inactive disease and ASDAS CII analyses due to no available CRP and BASDAI components.

*peripheral arthritis was defined as either ≥1 swollen joint in either 28 or 66 joint counts at baseline or "yes" in the question regarding arthritis in the ASAS criteria.

**2009 was chosen as the first three bDMARDs (adalimumab, etanercept and infliximab) were then well-established treatment options across the European countries. 2015 was chosen as secukinumab was approved as the first non-TNFi bDMARD treatment option that year.

***Continuous independent variables were categorized based on quartiles following the variable selection process;.

****Aldrich-Nelson pseudo R^2 index with Veall-Zimmermann correction[26], ASDAS: Ankylosing Spondylitis Disease Activity Score; AUROC: Area under the Receiver Operating Curve; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; Q1-Q6: question 1–6; BASFI: Bath Ankylosing Spondylitis Function Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: Body Mass Index; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; HLA-B27: Human Leukocyte Antigen subtypes B*2701–2759; TNFi: Tumor Necrosis Factor alpha inhibitor; OR: odds ratio; 95CI: 95% confidence interval.

treatment start, smoking, higher HAQ and BASDAI fatigue score were negative predictors, while BASDAI spinal pain and TNF start year 2015–2018 showed an inconsistent direction across outcomes. HAQ, smoking and BASDAI spinal pain score were common predictors although selected in less than half of the individual registries, see Tables 2-5.

The fit as assessed by the pseudo R^2 was 0.31, 0.41 and 0.12 for ASDAS inactive disease, ASDAS CII and 12-month drug retention, respectively. The performance of the final models as assessed by the AUROC was 0.76 (ASDAS inactive disease), 0.80 (ASDAS CII) and 0.66 (12-month drug retention), see Table 5.

In the pooled analyses *stratified* according to the proportion of patients achieving ASDAS inactive disease, ASDAS CII and 12-month drug retention, the pattern for male sex, HLA-B27, CRP, age at treatment start, smoking, HAQ, BASDAI fatigue and spinal pain and TNF start year was similar to what was observed in the pooled *unstratified* analyses, see Tables 5 and S7.

Discussion

In this study, we identified common predictors of TNFi treatment response and retention, applying the ASDAS as endpoint in a large scale analysis across 15 European countries through the EuroSpA collaboration.

Our main findings from the pooled analyses were that male sex, HLA-B27 positivity and high baseline CRP levels were positive predictors of ASDAS inactive disease, ASDAS CII and 12-month TNFi retention, while higher age at treatment start, current smoking, higher HAQ and higher baseline BASDAI fatigue scores were negative predictors. BASDAI spinal pain and TNF start year showed an inconsistent association across outcomes.Another finding was that in the pooled analyses of ASDAS inactive disease, 4 additional baseline predictors were identified, compared to the 8 that had been selected in at least half of the individual registries in which the variable was available. In the pooled analyses of ASDAS CII and 12-month drug retention, an additional 8 and 5 baseline predictors were identified (in addition to age that was forced in the model), respectively.

In the EuroSpA research collaboration, we have previously shown how baseline characteristics and treatment outcomes differ across European countries, which is a concern when attempting to pool data from different registries [3,19]. In the per registry analyses, however, the direction of the selected predictors rarely took opposite directions, and in the pooled cohort stratified according to proportions achieving remission, response, or 12-month drug retention, the selected predictors and their direction were similar to the ones identified in the pooled but unstratified cohort. We therefore suggest that despite the heterogeneity in patient populations, pooling of the registry cohorts to allow large scale analyses is viable. Moreover, we interpret the findings as an indication that the baseline predictors emerging from our pooled analyses might be considered universal across different axSpA populations.

Several studies have examined patient-reported indices (BASDAI and ASAS response criteria) or drug retention as measures of treatment response, and in line with our results, the majority have found male sex, elevated CRP, HLA-B27 positivity and younger age predictive of a better treatment response [9,17,31–33]. Our study adds to the literature by confirming previously established predictors to be common predictors for a large number of heterogeneous European registries. Moreover, by applying the more objective ASDAS as outcome in this large cohort, we have added weight to previous conclusions drawn from studies using patient-reported response criteria such as the BASDAI and ASAS.

As different response measures and baseline characteristics have been incorporated in previous studies investigating predictors of a response to TNFi, the general comparability with our results is hampered. Four studies that have included ASDAS as a measure of response, among other differences, report on different treatment lengths than our study: the most recent, a British study on 335 patients with axSpA, found that a poor ASDAS response after 14 weeks was mainly driven by adverse socioeconomic factors, comorbidity, poor health-related quality of life (HRQoL) and female sex, whereas clinical and patient-reported indices such as CRP, peripheral joint involvement, BASFI and BASDAI were less important [18]. Two Swiss studies on patients initiating TNFi and followed for one-year found that women had poorer ASDAS responses compared to men when adjusting for various clinical covariates [16,29]. A multicenter RCT including 311 patients with AS found that the strongest predictors of long-term remission on adalimumab treatment was an ASDAS response at 12 weeks, while baseline clinical characteristics were non-significant [30]. Our results are in agreement with these previous studies in finding that men achieve better ASDAS responses. Unfortunately, we could not reassess the British findings [18] as socioeconomic factors, HRQoL and comorbidities were not available in our analyses.

The BASDAI has been included as a baseline variable in the majority of previous studies but with conflicting or non-significant results [9,17,31]. As the BASDAI includes different symptoms thought to illustrate disease activity in axSpA, we suspected each component to associate differently with the outcomes, and therefore chose to analyze each component separately. We found that a higher BASDAI fatigue score at baseline consistently decreased the chance of remission, response and drug retention, while the other components showed conflicting results. A possible explanation for this differing pattern is that fatigue may be an easier entity to separate from the other features included in the BASDAI, and thereby more uniformly reported. Our findings are in line with two previous studies that reported an association between lower baseline patient fatigue scores and better treatment outcomes [4,34].

In a recent systematic literature review including 3917 patients, evidence regarding smoking habits as a predictor of treatment response in axSpA was inconclusive [35]. In our study, in contrast, smoking was a consistently negative predictor of treatment response, which is important because smoking is a potentially modifyable behavior. Our study thus adds substantial new evidence to the current body of knowledge regarding the role of smoking in the treatment of axSpA.

We found that starting TNFi from 2015 to 2018 versus 2009–2014 reduced the odds for staying on treatment while increasing the odds for achieving ASDAS inactive disease and CII. We interpret these findings as an indication that, as no alternatives to TNFi treatment existed in the earlier time period, patients stayed longer on treatment although the chance of achieving remission and response was lower. Patients starting TNFi before 2009 were excluded, as recent data have suggested that drug retention rates have changed considerably over time [36].

Strengths include the availability of similar clinical variables in 15 different European rheumatology registries that collect real-world data. This allowed us to investigate to which degree common predictors of treatment response (primarily ASDAS inactive disease) could be identified. Limitations include the observational nature of the current study, which does not allow any causal conclusions to be drawn. In addition, selection bias based on data availability cannot be ruled out; However, a comparison of baseline data for patients with versus without follow-up data showed no important differences. The unbalanced sizes of the registries may on one hand infer a risk of selecting a number of irrelevant predictors for larger registries and on the other hand lead to unreliable results for the smaller registries in the per-registry analyses. Besides, large registries may drive the selection of predictors in the pooled analyses. The level of data missingness and the variation of missingness across variables and registries is probably the most important limitation in our study. By applying multiple imputation, missing data were addressed in the best possible way, though the potential barriers of this approach must be kept in mind, e.g. variables may not be missing at random or may have been imputed although not available in specific registries.

Finally, we primarily investigated predictors of short- and medium-term outcomes, i.e. after 6 and 12 months, which is a limited window for a disease as axSpA with fluctuating disease activity over time. To give

a fuller picture of treatment effect, an aim for future studies could be to widen the time-window and/or investigate the maintenance of remission over time, e.g. by assessing remission rates at all registered visits in that time window.

The fit and the performance of the final models were found acceptable for ASDAS inactive disease and ASDAS CII but poor for 12-month drug retention. This suggests that especially for drug retention, it is likely that additional factors such as socioeconomic parameters, comorbidities and biomarkers (imaging and serological) are still needed for better prediction. In EuroSpA we are currently investigating the options to include biomarkers and comorbidities in future studies.

In conclusion, nine common baseline predictors of remission, response and drug retention in patients with axSpA treated with TNFi were identified across 15 European registries. The consistency of baseline predictors despite heterogeneity in patient populations and treatment practices, indicate that the predictors may be universal across different axSpA populations.

Data availability statement

The data in this article was collected in the individual registries and made available for secondary use through the EuroSpA Research Collaboration Network [https://eurospa.eu/#registries] Relevant patient level data may be made available on reasonable request to the corresponding author, but will require approval from all contributing registries.

Statement of clinical significance

What was already known before this study:

Cross-country differences in baseline characteristics and treatment outcomes in patients with axial spondyloarthritis initiating their first TNFi have previously been reported; such differences may contribute to the inconsistency in observed baseline predictors across single country studies.

What this study adds

Common baseline predictors of treatment response and drug adherence to TNFi across 15 European registries could be identified, indicating that these predictors may be considered universal across different axSpA populations.

Funding

This work was supported by Novartis Pharma AG.

Declaration of Competing Interest

LMØ, LL, SG and SHR: research grants from Novartis; UL: none; DDG none; JKW: consultant of AbbVie, Amgen, Celgene, Eli Lilly and Novartis; BG: research grants from Pfizer, Abbvie and BMS; LP: consultant of Novartis Finland, UCB Pharma, Pfizer, Sanofi, BMS, AbbVie, Amgen, Celgene, Eli Lilly, Boehringer-Ingelheim, Mylan; KL: consulting and/or speaking fees from Amgen, Johnson and Johnson and Novartis; ACo: research grants, consulting and/or speaking fees from Amgen, Lilly, Pfizer, Boehringer Ingelheim; KP: speaker and consulting fees from Pfizer, MSD, BMS, UCB, Amgen, Egis, Roche, AbbVie; JZ: speaker and consulting fees from Abbvie, Elli-Lilly, Sandoz, Novartis, Egis, UCB; EKK: none; NA: speaking fees from Pfizer; ÖSG: none; HS: research grant from Sociedade Portuguesa de Reumatologia and speaker and/or consultancy fees from Abbvie, Janssen, Lilly, Novartis and Pfizer; MJN: consulting and/or speaking fees from AbbVie, Eli Lilly, Janssens, Novartis and Pfizer; BM: research grant from Novartis; GTJ: research grants from AbbVie, Pfizer, UCB, Amgen, GSK. Speaker fee from Janssen; HR: consulting and/or speaking fees from Abbvie, Celgene, Pfizer, UCB, and Viatris; MT: consulting and/or speaking fees from Abbvie, Amgen, Biogen, Eli Lilly, Janssen, Medis, MSD, Novartis, Pfizer, Sanofi, Sandoz-Lek; AJG: none; IHB: Consultant for Abbvie, UCB, MSD, Novartis, Lilly, unrestricted Grants received for investigator initiated studies from: MSD, Pfizer, AbbVie, UCB, fees received for Lectures from BMS, AbbVie, Pfizer, MSD ; JA: PI for agreements between Karolinska Institutet and Abbvie, Astra-Zeneca, BMS, Eli Lilly, Janssen, MSD, Pfizer, Roche, Samsung Bioepis, Sanofi, and UCB; FI: consulting and/or speaking from Abbvie, Amgen, AstraZeneca, BMS, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Roche and UCB; AGL: Research Grant from Novartis, and speaker and/or consultancy fees from AbbVie, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, and UCB; ACi: consulting and/or speaking fees from AbbVie, Eli Lilly, Merck Sharp & Dohme, Novartis and Pfizer; MJS: speaker fees from Abbvie, AstraZeneca, Lilly, Novartis and Pfizer; CC: Speaker and consultancy fees from AbbVie, Amgen, Boehringer Ingelheim, Ewopharma, Lilly, Novartis, Pfizer; ZR: speaker or consultancy fees from Abbvie, Novartis, MSD, Medis, Biogen, Eli Lilly, Pfizer, Sanofi, Lek, Janssen; BjG: consulting and/or speaking fees from Amgen and Novartis; MØ: research grants from Abbvie, BMS, Merck, Celgene and Novartis, and speaker and/or consultancy fees from Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Hospira, Janssen, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi and UCB; MLH: Research grants from Abbvie, Biogen, BMS, Celltrion, Eli Lilly, Janssen Biologics B.V, Lundbeck Fonden, MSD, Medac, Pfizer, Roche, Samsung Biopies, Sandoz, Novartis.

Acknowledgments

The EuroSpA Research Collaboration Network was financially supported by Novartis Pharma AG. Novartis had no influence on the data collection, statistical analyses, manuscript preparation or decision to submit the manuscript. Professor Gary Macfarlane (University of Aberdeen) is Chief Investigator of BSRBR-AS and facilitated access to the UK data used in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152081.

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