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ORIGINAL RESEARCH

Early axial spondyloarthritis according to the ASAS consensus definition: characterisation of patients and effectiveness of a first TNF inhibitor in a large observational registry

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ABSTRACT

Objective To characterise the population fulfilling the Assessment of SpondyloArthritis international Society (ASAS) consensus definition of early axial spondyloarthritis (axSpA) and to determine the effectiveness of a first tumour necrosis factor inhibitor (TNFi) in early versus established axSpA in a large observational registry.

Methods A total of 3064 patients with axSpA in the Swiss Clinical Quality Management registry with data on duration of axial symptoms were included (≤2 years=early axSpA, N=658; >2 years=established axSpA, N=2406). Drug retention was analysed in patients starting a first TNFi in early axSpA (N=250) versus established axSpA (N=874) with multiple-adjusted Cox proportional hazards models. Adjusted logistic regression analyses were used to determine the achievement of the ASAS criteria for 40% improvement (ASAS40) at 1 year.

Results Sex distribution, disease activity, impairments of function and health-related quality of life were comparable between patients with early and established axSpA. Patients with established disease were older, had more prevalent axial radiographical damage and had a higher impairment of mobility. A comparable TNFi retention was found in early versus established disease after adjustment for age, sex, human leucocyte antigen-B27 status, education, body mass index, smoking, elevated C reactive protein and sacroiliac inflammation on MRI (HR 1.05, 95% CI 0.78 to 1.42). The adjusted ASAS40 response was similar in the two groups (OR 1.09, 95% CI 0.67 to 1.78). Results were confirmed in the population fulfilling the ASAS classification criteria.

Conclusion Considering the recent ASAS definition of early axSpA, TNFi effectiveness seems comparable in early versus established disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Assessment in SpondyloArthritis international Society (ASAS) has recently developed a consensus definition for early axSpA, with up to 2 years of axial symptom duration as a mainstay for use in research settings.

⇒ In previous analyses, different definitions of *early* axial spondyloarthritis (axSpA) were used, and earlier treatment was not associated with a better response to biological disease-modifying antirheumatic drugs.

WHAT THIS STUDY ADDS

⇒ This investigation in a large real-life cohort characterises the population with axSpA fulfilling the ASAS definition of early axSpA.

⇒ Initiating a first tumour necrosis factor inhibitor during the early disease phase, as newly defined by the ASAS, seems not to lead to better drug retention or better response rates compared with a later start of treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ If the results can be replicated in other cohorts, analyses using shorter cut-offs of axial symptom duration are warranted.

INTRODUCTION

The concept of a 'window of opportunity' is well accepted for rheumatoid arthritis (RA).[1] It summarises the findings that treatment with disease-modifying antirheumatic drugs (DMARDs) has an increased potential of preventing functional impairment and radiographical damage in RA if it is initiated within 1–2 years after diagnosis.[2] Whether a similar concept holds true for axial spondyloarthritis (axSpA) remains open,[3] as early treatment with biological (b)DMARDs was not consistently

associated with better outcomes.[4] Whether the failure to demonstrate a better response to bDMARDs in early treatment in axSpA might be due to the large heterogeneity of the definition of early disease used in the respective analyses remains unclear. Early axSpA was identified in a recent review of the literature by short symptom duration or short disease duration, with cut-offs ranging from 5 to 10 years, or based on the absence of radiographical sacroiliitis.[5] The Assessment in SpondyloArthritis international Society (ASAS) has, therefore, recognised the need for a standardised definition of 'early axSpA' and has recently published a consensus definition for research purposes: 'early axSpA' is defined as duration of ≤2 years of axial symptoms in patients already diagnosed as having axSpA, irrespective of the presence of radiographical axial damage.[6] The definition is complemented by a statement that axial symptoms should include spinal/buttock pain or morning stiffness and that their presence should be considered by a rheumatologist as related to axSpA.[6] The proposed consensus definition of early axSpA and its cut-off of 2 years are recognised as ambitious,[6] as the diagnostic delay in axSpA in clinical practice is still very long.[7] Moreover, there is currently no scientific evidence to support either the chosen cut-off or the start of axial symptoms as mainstays of the definition.[6] Therefore, we aimed at characterising the population fulfilling the new definition of early axSpA in a large cohort with available information on the start of first symptoms and also on the start of axial symptoms, as registered by the treating rheumatologist, to better evaluate the feasibility of its use for current research. In a second step, we used the new definition to analyse the effectiveness of treatment with a first tumour necrosis factor inhibitor (TNFi) in early axSpA compared with established axSpA.

METHODS

Characterisation of patients with early axSpA at inclusion in the Swiss Clinical Quality Management axSpA cohort

We took advantage of a large ongoing cohort of patients diagnosed with axSpA and recruited between 1 January 2004 and 1 June 2023 in the Swiss Clinical Quality Management (SCQM) registry.[8] The treating rheumatologists in private practices, non-academic hospitals and academic institutions[9] enter the date of first symptoms and are then asked to enter the presence of back pain of ≥3 months' duration (yes or no) after interpretation of the patient's history in the online database. If the answer is yes, the rheumatologist is prompted to specify several items on a list to establish the presence of an inflammatory back pain (IBP) character according to the criteria of ASAS,[10] followed by the starting date of axial symptoms.

In comparison with the ASAS definition of early axSpA, which stipulates that axial symptoms should include spinal/buttock pain *or* morning stiffness, patients with complete absence of axial pain and only presenting with morning stiffness were not included here. Moreover, only patients with ≥3 months of axial symptom duration are considered, which is not an absolute requirement of the ASAS definition of early axSpA. For both reasons, we might have slightly underestimated the actual proportion of early axSpA in SCQM.

Rheumatologists enter data on peripheral and axial manifestations, with information stratified by clinical, radiographical and magnetic resonance-tomographical assessments, only if the respective manifestation is present. The number of imaging procedures performed that yielded negative results and the number of procedures with unknown findings are therefore not known.

Clinical assessments are performed according to the recommendations of ASAS.[11] Data on bDMARDs and conventional synthetic DMARDs are entered by the rheumatologist with start and end dates. Data on the use of non-steroidal antirheumatic drugs (NSAIDs) are available as yes or no at the visit level. Laboratory examinations include C reactive protein (CRP) levels and human leucocyte antigen-B27 (HLA-B27) status.

Patients diagnosed as having axSpA were included in the early axSpA characterisation part of the study if information on the starting time point of axSpA-related back pain of at least 3 months' duration was registered in SCQM by the treating rheumatologist. Patients fulfilling the 2009 ASAS classification criteria for axSpA[12] were included in sensitivity analyses. As 1 January and 1 June were indicated as starting dates of axial symptoms in a higher number of instances than expected, it was considered a proxy for not exactly knowing the date within the respective year. We interval-censored all affected dates by assuming the onset date to fall into the reported onset year, and patients were only included if a differentiation between early and non-early axSpA was still possible (2.7% of patients excluded). In instances not affecting differentiation between early and non-early disease, inexact back pain onset dates (knowledge of month and year or only year of start) were mid-imputed. With regard to patient characteristics, missing variables were replaced by values from the closest visit within a range of 150 days before and 100 days after the considered time point (90 days before and 10 days after for disease activity variables). HLA-B27 status and data on family history were mapped from any other visit.

Effectiveness of TNFi treatment in early versus established axSpA

The effectiveness of TNFi treatment was assessed in patients starting a first TNFi after inclusion in SCQM. Drug retention was considered the primary outcome, and we estimated the time individual patients with axSpA maintained their first TNFi treatment when started in early versus established axSpA. Observations were censored at the last visit recorded in SCQM, the last change in medication dosage registered or the patient's last confirmation of TNFi use via the web-based mySCQM application,[13] whatever occurred last. Treatment response, defined as either the proportion of patients achieving the ASAS criteria for 40% improvement (ASAS40) or reaching a 50% reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50),

was assessed in exploratory analyses in patients with available disease activity measurement at 1 year (±6 months). Patients who had discontinued their first TNFi in the meantime were considered non-responders (response/tolerance analysis).[14]

Statistical analyses

Baseline characteristics between patients with early versus established axSpA were compared using the Kruskal-Wallis rank-sum test for continuous variables and the X^2 test for categorical variables. Tests were two sided, with a significance level set at 0.05. Log-rank tests are provided to compare the crude time to treatment discontinuation in early versus established axSpA. The following variables were introduced in multiple-adjusted Cox proportional hazards models to estimate differences in drug retention between early and established disease: age (continuous), sex (female vs male), HLA-B27 status (negative vs positive) and education (vocational and academic vs compulsory, respectively). These variables were considered confounders of our analysis as they may affect not only the outcome but also the exposure (the fact that a patient might be diagnosed earlier and TNFi initiated within 2 years following the start of axial symptoms). The number of missing values per covariate was N=63 for HLA-B27 and N=140 for education. Baseline characteristics are also shown for the population without missing covariates. Ankylosing Spondylitis Disease Activity Score (ASDAS) was added to the main model in a sensitivity analysis. In a further analysis, we added body mass index (BMI), current smoking status, the presence of elevated CRP and the presence of inflammatory MRI changes to the main model. We also checked for the presence of an interaction term between sex and early versus established disease. Event dates were interval-censored to account for the uncertainty of incomplete medication stop dates.

The significance of the unadjusted differences in BASDAI50 and ASAS40 responses was assessed using the Fisher's exact test. Logistic regression analysis was used to estimate an adjusted ratio for ASAS40 and BASDAI50, with adjustments for age, sex, HLA-B27, and education in the main model and additional adjustments for BMI, current smoking status, the presence of elevated CRP, and the presence of inflammatory MRI changes in a sensitivity analysis. All drug retention and treatment response analyses were performed in all patients diagnosed with axSpA and in the population fulfilling the ASAS axSpA classification criteria.

R statistical software was used for the statistical analyses. Artificial intelligence was only used to check the English grammar in the manuscript (QuillBot).

RESULTS

Characterisation of early axSpA at inclusion in SCQM

Patient disposition in the SCQM axSpA cohort is displayed in figure 1. Out of 3604 patients diagnosed with axSpA by their treating rheumatologist and having information on the start of axial symptoms, 658 patients

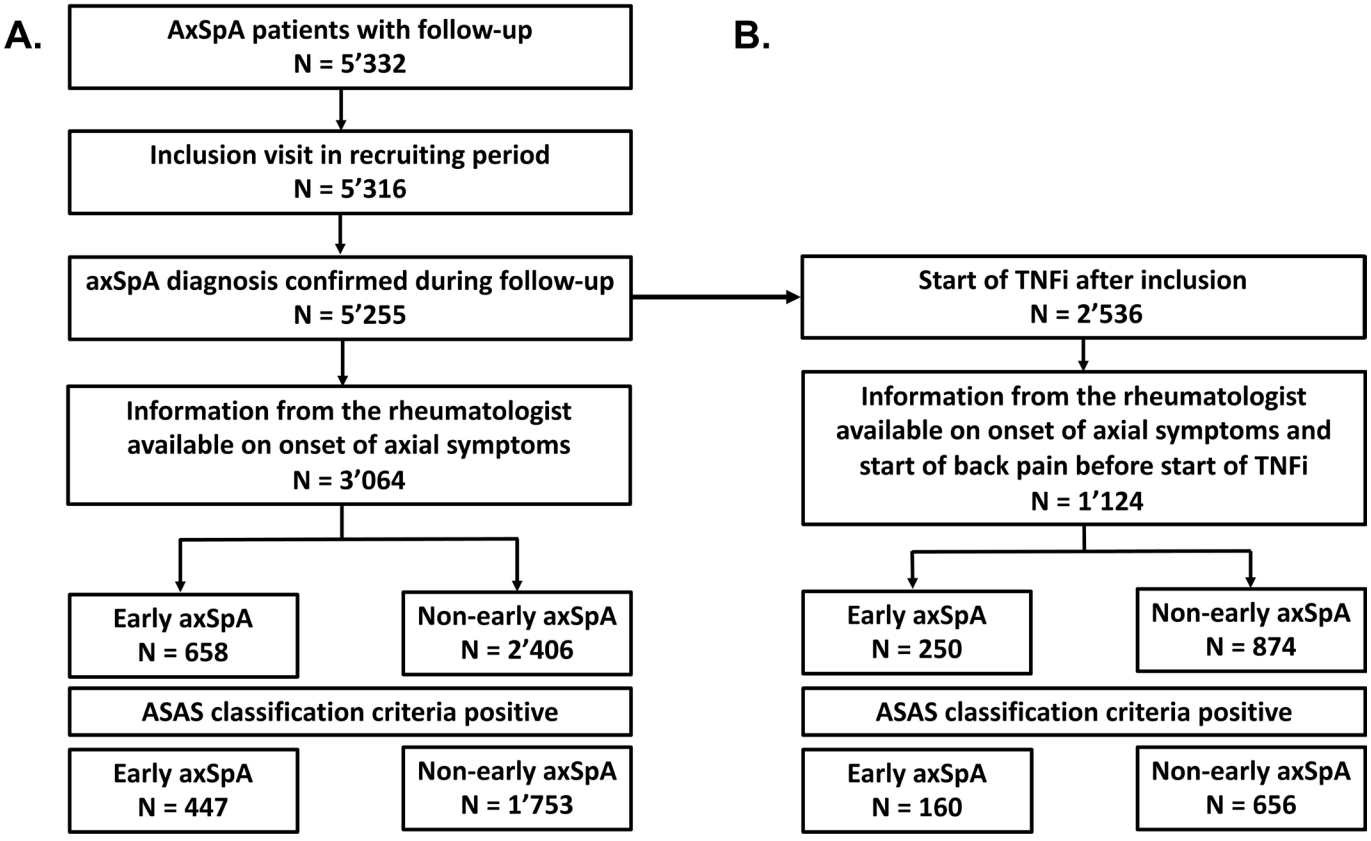

Figure 1 Patient disposition at inclusion in the SCQM cohort (A) and at start of a first TNF inhibitor (TNFi) (B). ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; SCQM, Swiss Clinical Quality Management; TNF, tumour necrosis factor.

had axial symptom duration ≤2 years and were classified as having early axSpA[6] at the time point of inclusion in SCQM (21.5%). In the population fulfilling the ASAS classification criteria,[12] the proportion of patients with early axSpA was 20.3% (N=447 for early disease and N=1753 for established disease). The percentage of early axSpA inclusions per year was constant at around 20%, irrespective of the number of patients fulfilling the ASAS classification criteria included per year since the initiation of the registry (figure 2). The median (IQR) duration since the start of axial symptoms was 0.8 (0.5–1.2) years in early axSpA and 10.1 (5.4–19.0) years in established axSpA (p<0.001; table 1). The median duration since the start of axial symptoms was comparable in the subgroup fulfilling the ASAS classification criteria (table 1). Time from onset of back pain to inclusion is shown for individual patients fulfilling the ASAS classification criteria in figure 3, stratified by early versus established disease. When the start of first symptoms rather than axial symptoms was considered, the median (IQR) symptom duration was only slightly longer: 1.3 (0.8–2.0) years in early axSpA and 10.5 (5.6–19.3) years in established axSpA (p<0.001). While axial symptoms corresponded to the first symptoms in the majority of patients with early axSpA, the time from the first symptom to axial symptoms varied in the remaining population, as shown for individual patients in the online supplemental figure 1. In the population fulfilling the ASAS classification criteria, the disease started with non-axial symptoms in a total of 170 patients with early axSpA (38.0%) and 209 patients with established axSpA (11.9%). The exact nature of these non-axial symptoms is not recorded in SCQM to allow a more detailed analysis.

Further, demographic, clinical and imaging characteristics of patients with axSpA with early disease are compared with those of established disease at inclusion for all patients with axSpA and those fulfilling the ASAS classification criteria in table 1. No significant differences could be observed with regard to sex, family history of axSpA or educational level. A trend for a lower proportion of patients being HLA-B27 positive was found in early axSpA, not reaching statistical significance. A lower proportion of patients with early axSpA compared with patients with established axSpA was recruited in academic hospitals, corresponding to the referral bias observed in tertiary institutions. Around 50% of patients with early and established axSpA were included in private rheumatology practices. Peripheral arthritis and uveitis were more often recorded in established disease, while enthesitis, psoriasis and inflammatory bowel disease were comparably distributed between the groups. Regarding axial disease, the majority of patients presented with IBP, although their proportion was higher in established disease (80.6% vs 70.0% in early disease, p<0.001). Inflammatory sacroiliac MRI involvement was more often reported in early disease, while axial radiographical involvement was more frequently registered in established disease. Rheumatologists indicated the presence of sacroiliac radiographical involvement in around 20% of patients with early disease. Mirroring higher radiographical involvement in later disease, spinal mobility as assessed by the Bath Ankylosing Spondylitis Mobility Index (BASMI) was lower in early versus established axSpA. In contrast, disease activity (BASDAI, ASDAS), as well as impairments in function and in health-related quality of life, were comparable in early versus established axSpA (table 1). Ninety per cent of patients with early axSpA were treated with NSAIDs at inclusion, while 25% of patients were already on TNFi treatment. The proportion of patients with established axSpA on current TNFi use was 36%. Only a few patients were on interleukin-17 inhibitors at inclusion in SCQM.

Drug retention analyses

The selection of patients for the retention analyses of a first TNFi is depicted in figure 1B. A total of 1124 patients with axSpA started their first TNFi after inclusion in SCQM and had available data on the start of axial symptoms (250 patients with axial symptom duration ≤2 years at TNFi start (early axSpA; 22%) and 874 patients with longer back pain duration at treatment start (established axSpA)). The baseline characteristics of these patients are shown in table 2. The differences between the two groups were comparable with those at inclusion in SCQM. As expected, patients initiating TNFi treatment had, in comparison with the population at inclusion, higher disease activity levels and a more severe impairment of function and quality of life. Median TNFi retention was slightly shorter in early axSpA (2.0 years; 95% CI 1.4 to 2.8) compared with established axSpA (2.3 years; 95% CI 2.1 to 2.8, log-rank test p=0.04). The reasons for discontinuation included adverse events (15.1%), insufficient response (40.7%), remission (4.0%) and other reasons (15.5) with no differences found between early and established axSpA (online supplemental table 1). The baseline characteristics of patients starting a first TNFi in early versus later disease were confirmed in the population fulfilling the ASAS classification criteria for axSpA (table 2).

The estimated unadjusted HR to discontinue a first TNFi was slightly higher in early versus later axSpA (1.22, 95% CI 1.03 to 1.44). Baseline characteristics of patients with complete data in the adjusted analyses were comparable to all patients included in the retention analysis (table 3). The difference in retention between early and established disease lost significance in the adjusted model 1 (HR 1.07, 95% CI 0.87 to 1.31, table 4). TNFi retention in the two groups further aligned with each other after additional adjustment for ASDAS or, alternatively, for BMI, current smoking, elevated CRP and inflammatory sacroiliac changes on MRI (adjusted models 2 and 3 in table 4). Female sex and HLA-B27 negativity were associated with a higher risk of TNFi discontinuation in these models, while a higher ASDAS or an elevated

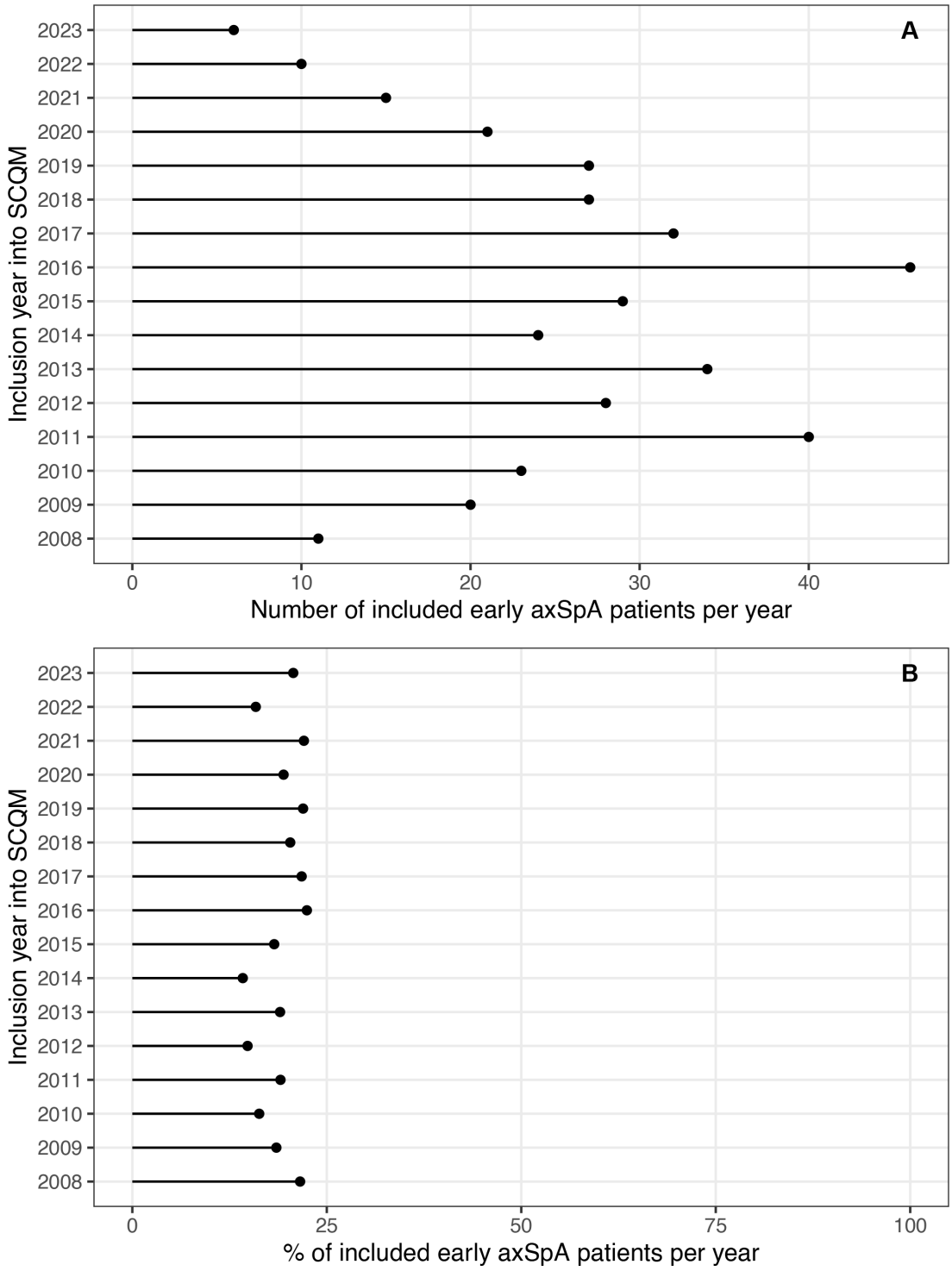

Figure 2 Number of patients with axSpA with early disease fulfilling the ASAS classification criteria included every year in SCQM (A). Proportion of patients with early axSpA for each inclusion year (B). ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; SCQM, Swiss Clinical Quality Management.

CRP was associated with longer drug retention (table 4). We found no interaction between sex and early versus established disease (online supplemental table 2), indicating that the differences in TNFi retention between women and men were comparable in early and later axSpA.

Treatment response analyses

Response rates at 1 year of treatment with a first TNFi were available in 577 patients for ASAS40 and 570 patients for BASDAI50. We found numerically slightly lower response rates in early versus established disease in unadjusted analyses: 34.4% vs 36.1% for ASAS40 (OR 0.93, 95% CI 0.61 to 1.40) and 32.5% vs 35.4% for BASDAI50 (OR 0.88, 95% CI 0.58 to 1.34). Statistical models adjusted

Table 1 Characteristics of patients with axSpA with early disease and established disease at inclusion in SCQM in the population fulfilling the ASAS axSpA classification criteria, as well as in all patients diagnosed as having axSpA

	All patients diagnosed as having axSpA (main analysis; N=3064)					Patients fulfilling the ASAS classification criteria (sensitivity analysis; N=2200)				
Parameter	N	Early disease (≤2 years) N=658	N	Established disease (>2 years) N=2406	P value	N	Early disease (≤2 years) N=447	N	Established disease (>2 years) N=1753	P value
Male sex, N (%)	658	334 (50.8)	2406	1242 (51.6)	0.73	447	242 (54.1)	1753	994 (56.7)	0.36
Age, years	658	38.0 (12.5)	2406	43.4 (12.2)	<0.001	447	33.2 (9.6)	1753	41.2 (11.4)	<0.001
Symptom duration, years, median (IQR)	651	1.3 (0.8–2.0)	2380	10.5 (5.6–19.3)	<0.001	440	1.3 (0.8–2.5)	1734	11.1 (5.9–20.4)	<0.001
Axial symptom duration, years, median (IQR)	658	0.8 (0.5–1.2)	2406	10.1 (5.4–19.0)	<0.001	447	0.8 (0.5–1.2)	1753	10.6 (5.6–20.0)	<0.001
Time since diagnosis, years, median (IQR)	652	0.3 (0.1–0.9)	2374	2.9 (0.6–8.6)	<0.001	441	0.3 (0.1–0.9)	1732	2.9 (0.5–9.5)	<0.001
HLA-B27 positive, N (%)	593	353 (59.5)	2179	1396 (64.1)	0.05	411	302 (73.5)	1637	1264 (77.2)	0.13
Family history axSpA, N (%)	578	110 (19.0)	2127	488 (22.9)	0.05	402	90 (22.3)	1567	401 (25.5)	0.21
Body mass index	580	25.1 (4.5)	2090	25.8 (4.7)	0.001	390	24.9 (4.6)	1555	25.7 (4.6)	<0.001
Education	516		1848		0.03	346		1374		0.17
Compulsory		69 (13.4)		337 (18.2)			47 (13.6)		245 (17.8)	
Vocational		292 (56.6)		963 (52.1)			191 (55.2)		719 (52.3)	
Academic		155 (30.0)		548 (29.7)			108 (31.2)		410 (29.8)	
Recruiting rheumatologist	658		2406		<0.001	447		1753		<0.001
Private practice		359 (54.6)		1303 (54.2)			217 (48.5)		918 (52.4)	
Non-academic hospital		182 (27.7)		505 (21.0)			142 (31.8)		394 (22.5)	
Academic hospital		117 (17.8)		598 (24.9)			88 (19.7)		441 (25.2)	
Back pain due to axSpA* ≥3 months, N (%)	658	2406 (100.0)	2406	2406 (100.0)	N/A	447	447 (100.0)	1753	1753 (100.0)	N/A
Inflammatory back pain, N (%)	649	454 (70.0)	2358	1900 (80.6)	<0.001	444	337 (75.9)	1719	1457 (84.8)	<0.001
Sacroiliitis ever*										
Clinical assessment, N (%)	638	422 (66.1)	2304	1409 (61.2)	0.02	436	313 (71.8)	1697	1138 (67.1)	0.07
Radiographical assessment, N (%)	640	121 (18.9)	2316	551 (23.8)	0.01	437	89 (20.4)	1700	481 (28.3)	0.001
MRI assessment (inflammation), N (%)	638	368 (57.7)	2304	979 (42.5)	<0.001	436	305 (70.0)	1697	884 (52.1)	<0.001
Spine involvement ever*										
Clinical opinion, N (%)	638	385 (60.3)	2307	1467 (63.6)	0.15	436	249 (57.1)	1699	1099 (64.7)	0.004
Radiographical assessment, N (%)	638	41 (6.4)	2307	267 (11.6)	<0.001	436	25 (5.7)	1699	218 (12.8)	<0.001
MRI assessment (inflammation), N (%)	638	196 (30.7)	2307	592 (25.7)	0.01	436	130 (29.8)	1699	478 (28.1)	0.53
ASAS classification criteria, N (%)	585	447 (76.4)	2000	1753 (87.6)	<0.001	447		1753		0.002
Only clinical arm		N/A		N/A			90 (20.1)		485 (27.7)	
Only imaging arm		N/A		N/A			164 (36.7)		531 (30.3)	
Clinical+imaging arm		N/A		N/A			193 (43.2)		737 (42.0)	

Continued

Table 1 Continued

Parameter	All patients diagnosed as having axSpA (main analysis; N=3064)					Patients fulfilling the ASAS classification criteria (sensitivity analysis; N=2200)				
	N	Early disease (≤2 years) N=658	N	Established disease (>2 years) N=2406	P value	N	Early disease (≤2 years) N=447	N	Established disease (>2 years) N=1753	P value
Ever peripheral arthritis, N (%)	654	251 (38.4)	2366	1023 (43.2)	0.03	446	149 (33.4)	1730	671 (38.8)	0.04
Ever enthesitis, N (%)	656	421 (64.2)	2389	1591 (66.6)	0.27	446	275 (61.7)	1744	1155 (66.2)	0.08
Ever uveitis, N (%)	525	46 (8.8)	1904	337 (17.7)	<0.001	355	38 (10.7)	1381	278 (20.1)	<0.001
Ever psoriasis, N (%)	502	54 (10.8)	1828	201 (11.0)	0.94	338	30 (8.9)	1328	134 (10.1)	0.57
Ever inflammatory bowel disease, N (%)	482	46 (9.5)	1783	170 (9.5)	1.00	330	26 (7.9)	1299	105 (8.1)	0.99
Physician global disease activity	633	3.9 (2.3)	2286	3.4 (2.2)	<0.001	428	3.9 (2.3)	1674	3.4 (2.2)	<0.001
Patient global disease activity	519	5.0 (2.7)	1872	4.9 (2.8)	0.32	342	5.0 (2.7)	1381	4.9 (2.8)	0.71
BASDAI	471	4.6 (2.2)	1713	4.6 (2.3)	0.73	313	4.5 (2.2)	1274	4.5 (2.3)	0.99
ASDAS	451	2.8 (1.0)	1576	2.8 (1.0)	0.13	304	2.8 (1.1)	1171	2.8 (1.1)	0.52
Elevated CRP, N (%)	604	209 (34.6)	2134	636 (29.8)	0.03	413	143 (34.6)	1564	515 (32.9)	0.55
CRP (mg/L), median (IQR)	609	5.0 (1.5–10)	2136	3.6 (1.0–8.0)	0.01	415	4.6 (1.5–9.0)	1565	4.0 (1.2–9.0)	0.30
BASFI	465	2.9 (2.5)	1679	3.0 (2.5)	0.64	307	2.8 (2.5)	1244	3.0 (2.5)	0.33
BASMI	585	1.4 (1.4)	2116	1.9 (1.8)	<0.001	402	1.3 (1.4)	1589	1.9 (1.9)	<0.001
EQ-5D	458	62.5 (20.9)	1647	63.9 (21.7)	0.11	301	64.2 (20.6)	1223	64.1 (22.1)	0.68
SF-12, physical component summary score	439	38.6 (10.5)	1586	39.2 (10.3)	0.27	287	39.6 (10.6)	1181	39.7 (10.4)	0.93
SF-12, mental component summary score	439	43.9 (11.1)	1586	43.8 (11.4)	0.99	287	43.5 (11.3)	1181	43.7 (11.5)	0.79
Non-steroidal antirheumatic drugs, N (%)	589	532 (90.3)	2099	1800 (85.8)	0.01	408	366 (89.7)	1574	1350 (85.8)	0.05
Conventional synthetic DMARDs, N (%)	658	74 (11.2)	2403	289 (12.0)	0.63	447	40 (8.9)	1751	176 (10.1)	0.54
Tumour necrosis factor inhibitors, N (%)	656	163 (24.8)	2401	855 (35.6)	<0.001	447	106 (23.7)	1749	567 (32.4)	<0.001
Interleukin-17 inhibitors, N (%)	658	3 (0.5)	2405	43 (1.8)	0.02	447	2 (0.4)	1752	19 (1.1)	0.34

Except where indicated otherwise, values represent the mean and SD.
*Information provided by the local rheumatologist with unknown total number of patients with imaging performed.
ASAS, Assessment in SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C reactive protein; DMARDs, disease-modifying antirheumatic drugs; EQ-5D, European Quality of Life 5-domains Questionnaire; HLA-B27, human leucocyte antigen-B27; N/A, not applicable; SCQM, Swiss Clinical Quality Management; SF-12, Short Form Questionnaire with 12 questions.

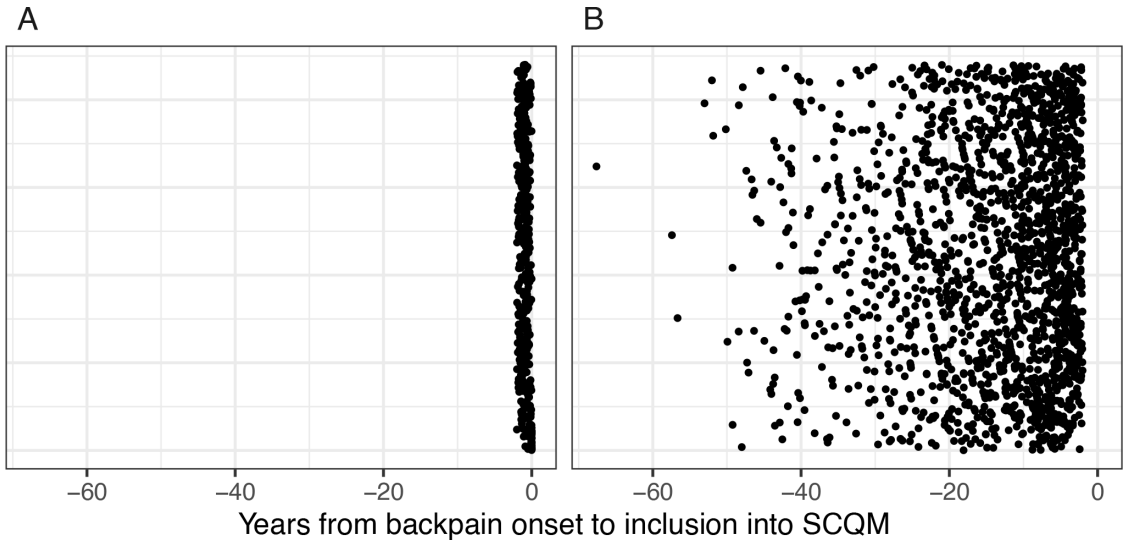

Figure 3 Years from start of axSpA-related axial symptoms to inclusion in SCQM shown for individual patients with axSpA fulfilling the ASAS classification criteria. (A) Early axSpA (≤2 years by definition); (B) established axSpA (>2 years by definition). Time point of inclusion in SCQM=0. ASAS, Assessment in SpondyloArthritis international Society; axSpA, axial spondyloarthritis; SCQM, Swiss Clinical Quality Management.

for potential confounders and additional explanatory variables are presented in table 5. No significant differences could be detected between patients with early and established disease for ASAS40 and BASDAI50 responses in these analyses. Male sex, HLA-B27 positivity, higher education and elevated CRP were consistently associated with significantly better response rates in these models (table 5). There was only a trend for inflammatory sacroiliac changes being associated with a better BASDAI50 response, which did not reach statistical significance and was not found for the ASAS40 response.

The results found in the whole population diagnosed with axSpA were confirmed in patients fulfilling the ASAS classification criteria (table 5). A higher BMI was associated with a significantly reduced treatment response according to BASDAI50 and ASAS40 criteria in this population.

DISCUSSION

This first analysis of patients with early axSpA according to the ASAS definition[6] in a large observational cohort revealed several important aspects. First, up to 20% of patients recruited over the past two decades had axial symptom duration of ≤2 years and fulfilled the new definition for early axSpA. Second, patients with early axSpA were very comparable with patients with longer axial symptom duration regarding important disease characteristics, with the exception of factors affected by time (such as age, radiographical damage and impairment of spinal mobility). Finally, the effectiveness of TNFi, assessed through the evaluation of their retention as well as ASAS40 and BASDAI50 response rates, was comparable in early and established axSpA.

The fact that 20% of patients recruited to SCQM fulfilled the definition of early axSpA is, on the one hand, reassuring. Although the median diagnostic delay in axSpA is still long,[7] a relevant proportion of patients in real-life clinical practice are diagnosed in this early disease stage, guaranteeing the feasibility of future studies using this definition, preconditioned that our results are confirmed in other healthcare systems. On the other hand, we could not identify a trend for earlier recognition of axSpA over the years, at least with regard to the proportion of patients identified within 2 years after the onset of axial symptoms. This highlights the need to intensify the already considerable international and national efforts to improve disease recognition.[15] The fact that the first symptoms were not axial symptoms in a significant number of patients fulfilling the ASAS consensus definition of 'early axSpA' indicates that the presence of peripheral or extramusculoskeletal manifestations might lead to an earlier recognition of axial disease. Indeed, a recent study found a high prevalence of both overall and previously undiagnosed SpA in patients with acute anterior uveitis.[16]

Important disease characteristics were comparable between the early and later stages of the disease: sex distribution, proportions of HLA-B27 positivity and of a positive family history of axSpA, markers of disease activity, function and health-related quality of life. Radiographical axial involvement and impairment of spinal mobility as assessed by the BASMI were, as expected, more prominent in established axSpA. Only a few earlier cohorts provide some comparison for the characteristics of our 658 patients with early axSpA at inclusion in SCQM. Inclusion criteria for a small cohort (N=68) from the Netherlands (ESpAC) comprised the presence of IBP of ≤2 years' duration with onset of back pain before the age of 40 years and persistence for at least 3 months.[17 18] Importantly, diagnosis of axSpA before inclusion was not

Table 2 Characteristics of patients with axSpA with early disease and established disease at start of first TNF inhibitor

Parameter	All patients diagnosed as having axSpA (main analysis; N=1124)					Patients fulfilling the ASAS classification criteria (sensitivity analysis; N=816)				
	N	Early disease (≤2 years) N=250	N	Established disease (>2 years) N=874	P value	N	Early disease (≤2 years) N=160	N	Established disease (>2 years) N=656	P value
Male sex, N (%)	250	127 (50.8)	874	447 (51.1)	0.98	160	86 (53.8)	656	362 (55.2)	0.81
Age, years	250	38.4 (12.9)	874	43.6 (12.3)	<0.001	160	33.3 (9.7)	656	40.9 (11.5)	<0.001
Symptom duration, years, median (IQR)	248	1.4 (0.8–2.4)	867	10.8 (5.9–19.7)	<0.001	159	1.4 (0.8–2.6)	651	11.2 (6.1–20.3)	<0.001
Axial symptom duration, years, median (IQR)	250	0.8 (0.5–1.3)	874	10.2 (5.3–19.0)	<0.001	160	0.8 (0.5–1.3)	656	10.4 (5.5–19.3)	<0.001
Time since diagnosis, years, median (IQR)	249	0.4 (0.2–0.9)	864	2.6 (0.5–8.9)	<0.001	160	0.3 (0.2–0.8)	649	2.8 (0.5–9.3)	<0.001
HLA-B27 positive, N (%)	223	123 (55.2)	804	533 (66.3)	0.003	140	97 (69.3)	613	467 (76.2)	0.11
Family history axSpA, N (%)	231	42 (18.2)	812	185 (22.8)	0.16	151	30 (19.9)	616	159 (25.8)	0.16
Body mass index	224	25.1 (4.5)	807	25.8 (4.6)	0.02	142	24.8 (4.7)	614	25.6 (4.6)	0.02
Current smoking	230	77 (33.5)	804	266 (33.1)	0.32	146	52 (35.6)	602	210 (34.9)	0.04
Education	203		721		0.39	133				0.83
Compulsory		31 (15.8)		124 (17.2)			22 (16.5)		87 (16.0)	
Vocational		124 (61.1)		402 (55.8)			77 (57.9)		303 (55.8)	
Academic		47 (23.2)		195 (27.0)			34 (25.6)		153 (28.2)	
Back pain due to axSpA* ≥3 months, N (%)	250	250 (100.0)	874	874 (100.0)	N/A	160	160 (100.0)	656	656 (100.0)	N/A
Inflammatory back pain, N (%)	236	173 (73.3)	816	689 (84.4)	<0.001	160	122 (76.2)	652	572 (87.7)	<0.001
Sacroiliitis ever*										
Clinical assessment, N (%)	226	149 (65.9)	766	522 (68.1)	0.59	151	112 (74.2)	615	435 (70.7)	0.46
Radiographical assessment, N (%)	229	40 (17.5)	773	203 (26.3)	0.01	154	31 (20.1)	621	181 (29.1)	0.03
MRI assessment (inflammation), N (%)	226	132 (58.4)	766	345 (45.0)	0.001	151	108 (71.5)	615	317 (51.5)	<0.001
Spine involvement ever*										
Clinical opinion, N (%)	227	148 (65.2)	770	533 (69.2)	0.29	152	99 (65.1)	619	434 (70.1)	0.27
Radiographical assessment, N (%)	227	13 (5.7)	770	104 (13.5)	0.002	152	8 (5.3)	619	89 (14.4)	0.004
MRI assessment, N (%)	227	80 (35.2)	770	222 (28.8)	0.08	152	48 (31.6)	619	186 (30.0)	0.79
ASAS classification criteria, N (%)	212	160 (75.5)	743	656 (88.3)	<0.001	160		656		0.01
Only clinical arm		N/A		N/A			27 (16.9)		145 (22.1)	
Only imaging arm		N/A		N/A			68 (42.5)		200 (30.5)	
Clinical+imaging arm		N/A		N/A			65 (40.6)		311 (47.4)	
Ever peripheral arthritis, N (%)	238	103 (43.3)	815	352 (43.2)	1.00	160	67 (41.9)	652	259 (39.7)	0.68
Ever enthesitis, N (%)	236	163 (69.1)	804	577 (71.8)	0.47	158	109 (69.0)	644	453 (70.3)	0.81
Ever uveitis, N (%)	190	18 (9.5)	642	101 (15.7)	0.04	125	14 (11.2)	517	87 (16.8)	0.16

Continued

Table 2 Continued

Parameter	All patients diagnosed as having axSpA (main analysis; N=1124)					Patients fulfilling the ASAS classification criteria (sensitivity analysis; N=816)				
	N	Early disease (≤2 years) N=250	N	Established disease (>2 years) N=874	P value	N	Early disease (≤2 years) N=160	N	Established disease (>2 years) N=656	P value
Ever psoriasis, N (%)	189	23 (12.2)	624	73 (11.7)	0.96	124	13 (10.5)	502	52 (10.4)	1.00
Ever inflammatory bowel disease, N (%)	181	17 (9.4)	614	55 (9.0)	0.98	121	12 (9.9)	497	38 (7.6)	0.53
Physician global disease activity	214	5.0 (1.9)	730	4.7 (1.8)	0.06	145	5.1 (2.0)	581	4.7 (1.9)	0.08
Patient global disease activity	180	6.1 (2.3)	627	6.1 (2.4)	0.48	122	6.0 (2.3)	498	6.1 (2.5)	0.31
BASDAI	172	5.6 (2.0)	612	5.4 (2.0)	0.28	118	5.6 (2.0)	483	5.3 (2.0)	0.11
ASDAS	157	3.3 (0.9)	549	3.3 (0.9)	0.48	109	3.3 (0.9)	440	3.3 (0.9)	0.25
ASDAS ≥2.1	157	143 (91.1)	549	498 (90.7)	1.00	109	99 (90.8)	440	399 (90.7)	1.00
Elevated CRP, N (%)	208	113 (54.3)	703	391 (55.6)	0.80	141	69 (48.9)	561	264 (47.1)	0.76
CRP (mg/L), median (IQR)	209	5.9 (2.0–14.0)	704	6.0 (2.0–13.0)	0.87	141	6.0 (2.0–14.0)	562	6.5 (2.0–14.0)	0.94
BASFI	170	3.7 (2.4)	598	3.7 (2.4)	0.88	118	3.8 (2.6)	474	3.6 (2.4)	0.57
BASMI	186	1.4 (1.3)	657	2.1 (1.9)	<0.001	128	1.3 (1.3)	524	2.0 (1.9)	<0.001
EQ-5D	167	56.2 (20.6)	586	58.6 (20.7)	0.13	116	56.7 (20.8)	465	59.5 (20.8)	0.16
SF-12, physical component summary score	153	35.4 (9.4)	543	36.1 (9.1)	0.41	107	36.0 (9.7)	434	36.8 (9.2)	0.37
SF-12, mental component summary score	153	40.9 (10.0)	543	42.3 (11.1)	0.19	107	40.2 (9.7)	434	42.2 (11.2)	0.10
Non-steroidal antirheumatic drugs, N (%)	150	144 (96.0)	515	488 (94.8)	0.69	98	96 (98.0)	411	391 (95.1)	0.34
Conventional synthetic DMARDs, N (%)	250	34 (13.6)	873	108 (12.4)	0.68	160	21 (13.1)	655	67 (10.2)	0.36

Except where indicated otherwise, values represent the mean and SD.
*Information provided by the local rheumatologist with unknown total number of patients with imaging performed.
ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C reactive protein; DMARDs, disease-modifying antirheumatic drugs; EQ-5D, European Quality of Life 5-domains Questionnaire; HLA-B27, human leucocyte antigen-B27; N/A, not applicable; SF-12, Short Form Questionnaire with 12 questions; TNF, tumour necrosis factor.

Table 3 Characteristics of patients with axSpA with early disease and established disease at start of first TNF inhibitor in the main adjusted retention analysis (model 1; patients without missing covariate data)

	All patients diagnosed as having axSpA (main analysis; N=843)					Patients fulfilling the ASAS classification criteria (sensitivity analysis; N=816)				
Parameter	N	Early disease (≤2 years) N=178	N	Established disease (>2 years) N=665	P value	N	Early disease (≤2 years) N=114	N	Established disease (>2 years) N=509	P value
Male sex, N (%)	178	95 (53.4)	665	333 (50.1)	0.49	114	64 (56.1)	509	275 (54.0)	0.76
Age, years	178	37.6 (13.0)	665	43.7 (12.3)	<0.001	114	32.4 (9.4)	509	41.5 (11.5)	<0.001
Symptom duration, years, median (IQR)	176	1.4 (0.8–2.6)	661	10.9 (5.9–19.8)	<0.001	113	1.5 (0.8–2.6)	506	11.2 (6.1–20.7)	<0.001
Axial symptom duration, years, median (IQR)	178	0.8 (0.5–1.2)	665	10.2 (5.2–19.2)	<0.001	114	0.8 (0.5–1.2)	509	10.7 (5.6–19.9)	<0.001
Time since diagnosis, years, median (IQR)	177	0.4 (0.2–1.0)	658	2.5 (0.5–8.9)	<0.001	114	0.3 (0.2–0.9)	503	2.6 (0.5–9.4)	<0.001
HLA-B27 positive, N (%)	178	104 (58.4)	665	437 (65.7)	0.09	114	82 (71.9)	509	384 (75.4)	0.51
Family history axSpA, N (%)	168	33 (19.6)	623	148 (23.8)	0.31	110	24 (21.8)	480	130 (27.1)	0.31
Body mass index	133	24.9 (4.4)	630	25.7 (4.5)	0.02	109	24.3 (4.4)	488	25.5 (4.4)	0.003
Current smoking, N (%)	177	63 (35.6)	655	227 (34.7)	0.79	113	43 (38.1)	502	184 (36.7)	0.36
Education	178		665		0.36	114		509		0.88
Compulsory		26 (14.6)		112 (16.8			17 (14.9)		80 (15.7)	
Vocational		110 (61.8)		371 (55.8)			67 (58.8)		286 (56.2)	
Academic		42 (23.6)		182 (27.4)			30 (26.3)		143 (28.1)	
Back pain due to axSpA* ≥3 months, N (%)	178	178 (100.0)	665	665 (100.0)	N/A	114	114 (100.0)	509	509 (100.0)	N/A
Inflammatory back pain, N (%)	164	122 (74.4)	630	535 (84.9)	0.002	114	87 (76.3)	507	449 (88.6)	0.001
Sacroiliitis ever*										
Clinical assessment, N (%)	159	109 (68.6)	593	417 (70.3)	0.74	109	83 (76.1)	482	351 (72.8)	0.56
Radiographical assessment, N (%)	161	31 (19.3)	597	163 (27.3)	0.048	111	25 (22.5)	485	145 (29.9)	0.15
MRI assessment (inflammation), N (%)	159	91 (57.2)	593	266 (44.9)	0.01	109	63 (67.0)	482	244 (50.6)	0.003
Spine involvement ever*										
Clinical opinion, N (%)	159	109 (68.6)	596	432 (72.5)	0.38	109	76 (69.7)	485	353 (72.8)	0.60
Radiographical assessment, N (%)	159	10 (6.3)	596	86 (14.4)	0.01	109	6 (5.5)	485	75 (15.5)	0.01
MRI assessment, N (%)	159	47 (29.6)	596	163 (27.3)	0.65	109	28 (25.7)	485	136 (28.0)	0.71
Ever peripheral arthritis, N (%)	166	75 (45.2)	627	280 (44.7)	0.97	114	52 (45.6)	506	208 (41.1)	0.48
Ever enthesitis, N (%)	165	110 (66.7)	619	446 (72.1)	0.21	113	76 (67.3)	500	357 (71.4)	0.45
Ever uveitis, N (%)	129	16 (12.4)	480	74 (15.4)	0.47	86	12 (14.0)	388	66 (17.0)	0.60
Ever psoriasis, N (%)	130	19 (14.6)	471	56 (11.9)	0.50	87	11 (12.6)	379	43 (11.3)	0.88
Ever inflammatory bowel disease, N (%)	123	12 (9.8)	466	42 (9.0)	0.94	84	9 (10.7)	375	31 (8.3)	0.61
Physician global disease activity	152	5.0 (1.9)	556	4.6 (1.8)	0.01	105	5.1 (2.0)	446	4.6 (1.8)	0.04

Continued

Table 3 Continued

Parameter	All patients diagnosed as having axSpA (main analysis; N=843)					Patients fulfilling the ASAS classification criteria (sensitivity analysis; N=816)				
	N	Early disease (≤2 years) N=178	N	Established disease (>2 years) N=665	P value	N	Early disease (≤2 years) N=114	N	Established disease (>2 years) N=509	P value
Patient global disease activity	142	6.0 (2.3)	535	6.1 (2.4)	0.35	97	5.9 (2.3)	427	6.1 (2.4)	0.31
BASDAI	138	5.5 (2.0)	529	5.4 (2.0)	0.87	95	5.5 (2.0)	420	5.3 (2.0)	0.41
ASDAS	130	3.3 (0.9)	484	3.3 (0.9)	0.70	90	3.3 (0.9)	392	3.2 (0.9)	0.39
ASDAS ≥2.1	130	119 (91.5)	484	440 (90.9)	0.96	90	82 (91.1)	392	355 (90.6)	1.00
Elevated CRP, N (%)	145	69 (47.6)	541	236 (43.6)	0.45	101	51 (50.5)	437	202 (46.2)	0.51
CRP (mg/L), median (IQR)	146	5.9 (2.9–16.0)	541	6.0 (2.0–13.0)	0.78	101	6.0 (2.0–18.0)	437	6.5 (2.0–14.0)	0.69
BASFI	138	3.7 (2.4)	521	3.7 (2.4)	0.97	95	3.7 (2.5)	416	3.6 (2.4)	0.73
BASMI	136	1.3 (1.3)	509	2.1 (1.9)	<0.001	96	1.2 (1.3)	410	2.0 (1.9)	<0.001
EQ-5D	138	56.7 (20.3)	511	59.1 (20.5)	0.10	95	57.2 (20.6)	408	60.4 (20.5)	0.09
SF-12, physical component summary score	131	35.6 (9.4)	477	36.2 (9.2)	0.49	91	36.3 (9.6)	386	37.0 (9.3)	0.47
SF-12, mental component summary score	131	40.7 (9.8)	477	42.3 (11.2)	0.15	91	39.8 (9.7)	386	42.5 (11.1)	0.03
Non-steroidal antirheumatic drugs, N (%)	114	110 (96.5)	396	377 (95.2)	0.74	75	74 (98.7)	321	306 (95.3)	0.32
Conventional synthetic DMARDs, N (%)	178	26 (14.6)	664	83 (12.5)	0.54	114	16 (14.0)	509	53 (10.4)	0.35

Except where indicated otherwise, values represent the mean and SD.
*Information provided by the local rheumatologist with unknown total number of patients with imaging performed.
ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C reactive protein; DMARDs, disease-modifying antirheumatic drugs; EQ-5D, European Quality of Life 5-domains Questionnaire; HLA-B27, human leucocyte antigen-B27; N/A, not applicable; SF-12, Short Form Questionnaire with 12 questions; TNF, tumour necrosis factor.

Table 4 Multiple adjusted Cox proportional hazards model for analysis of drug discontinuation of a first TNF inhibitor in early versus established axSpA

		Unadjusted analysis			Adjusted model 1			Adjusted model 2			Adjusted model 3		
Population	**Variable**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Main analysis: all patients diagnosed as having axSpA	Early vs established disease	**1.22**	**1.03; 1.44**	**0.02**	1.07	0.87; 1.31	0.51	1.00	0.79; 1.28	0.98	1.01	0.79; 1.29	0.91
	Age				1.00	0.99; 1.00	0.46	1.00	0.99; 1.00	0.41	0.99	0.98; 1.00	0.06
	Female sex				**1.56**	**1.31; 1.85**	**<0.001**	**1.51**	**1.24; 1.85**	**<0.001**	**1.51**	**1.22; 1.85**	**<0.001**
	HLA-B27 negativity				**1.39**	**1.16; 1.67**	**<0.001**	**1.40**	**1.13; 1.73**	**0.002**	**1.25**	**1.01; 1.54**	**0.04**
	Education vocational				0.83	0.66; 1.04	0.11	0.77	0.58; 1.01	0.06	0.83	0.64; 1.08	0.17
	Education academic				**0.77**	**0.60; 1.00**	**0.048**	0.82	0.61; 1.12	0.21	0.97	0.72; 1.30	0.81
	ASDAS							**0.82**	**0.74; 0.92**	**<0.001**			
	Body mass index										**1.03**	**1.00; 1.05**	**0.03**
	Current smoking										1.11	0.91; 1.37	0.30
	Elevated CRP										**0.58**	**0.47; 0.71**	**<0.001**
	Sacroiliitis on MRI										0.85	0.70; 1.03	0.10
	(Number of patients/events)	(1124/735)			(843/573)			(614/424)			(619/436)		
Sensitivity analysis: patients fulfilling the ASAS classification criteria	Early vs established disease	**1.31**	**1.06; 1.61**	**0.01**	1.23	0.95; 1.59	0.12	1.12	0.83; 1.52	0.44	1.05	0.78; 1.42	0.73
	Age				1.00	0.99; 1.01	0.61	1.00	0.99; 1.01	0.41	0.99	0.98; 1.00	0.04
	Female sex				**1.53**	**1.25; 1.87**	**<0.001**	**1.49**	**1.18; 1.87**	**<0.001**	**1.45**	**1.15; 1.83**	**0.002**
	HLA-B27 negativity				**1.40**	**1.12; 1.75**	**0.004**	**1.33**	**1.03; 1.72**	**0.03**	1.23	0.94; 1.60	0.13
	Education vocational				0.85	0.64; 1.11	0.23	0.76	0.55; 1.05	0.10	0.79	0.58; 1.08	0.14
	Education academic				0.93	0.69; 1.25	0.62	0.91	0.64; 1.30	0.61	1.02	0.72; 1.43	0.93
	ASDAS							**0.82**	**0.73; 0.93**	**0.002**			
	Body mass index										1.02	0.99; 1.05	0.12
	Current smoking										1.06	0.84; 1.33	0.62
	Elevated CRP										**0.54**	**0.43; 0.68**	**<0.001**
	Sacroiliitis on MRI										0.89	0.71; 1.12	0.33
	(Number of patients/events)	(816/526)			(623/419)			(482/328)			(488/340)		

Statistically significant results are shown in bold. The number of patients assessed and the number of treatment discontinuations are indicated for each statistical model at the bottom.
ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; CRP, C reactive protein; HLA-B27, human leucocyte antigen-B27; TNF, tumour necrosis factor.

Table 5 Multiple-adjusted response rate analyses at 1 year of treatment with a first TNFi for different outcomes in early versus established axSpA

		All patients diagnosed as having axSpA						Patients fulfilling the ASAS classification criteria					
		Adjusted model 1			Adjusted model 2			Adjusted model 1			Adjusted model 2		
Outcome	**Variable**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
ASAS40	Early vs established disease	1.09	0.67; 1.78	0.72	1.04	0.60; 1.77	0.89	0.80	0.45; 1.42	0.45	0.74	0.39; 1.36	0.33
	Age	0.99	0.97; 1.00	0.16	0.99	0.98; 1.01	0.44	0.98	0.96; 1.00	0.054	0.99	0.97; 1.01	0.32
	Female sex	**0.66**	**0.44; 0.98**	**0.04**	**0.60**	**0.38; 0.93**	**0.02**	0.73	0.47; 1.14	0.17	0.72	0.44; 1.17	0.19
	HLA-B27 negativity	**0.55**	**0.35; 0.84**	**0.01**	**0.60**	**0.37; 0.97**	**0.04**	**0.41**	**0.23; 0.70**	**0.002**	**0.49**	**0.27; 0.88**	**0.02**
	Education vocational	**2.00**	**1.08; 3.87**	**0.03**	**2.24**	**1.15; 4.62**	**0.02**	**2.22**	**1.09; 4.82**	**0.03**	**2.18**	**1.04; 4.87**	**0.047**
	Education academic	**2.35**	**1.22; 4.73**	**0.01**	**2.75**	**1.35; 5.92**	**0.01**	**2.35**	**1.11; 5.31**	**0.03**	**2.29**	**1.03; 5.35**	**0.047**
	Body mass index				0.95	0.90; 1.00	0.06				**0.94**	**0.89; 1.00**	**0.046**
	Current smoking				0.91	0.57; 1.43	0.67				1.04	0.63; 1.69	0.88
	Elevated CRP				**2.10**	**1.37; 3.24**	**<0.001**				**2.26**	**1.41; 3.64**	**<0.001**
	Sacroiliitis on MRI				1.23	0.80; 1.89	0.36				1.20	0.73; 1.96	0.47
	(Number of patients/events)	(489/172)			(433/153)			(388/141)			(348/130)		
BASDAI50	Early vs established disease	0.89	0.53; 1.47	0.73	0.73	0.41; 1.28	0.28	0.71	0.39; 1.26	0.25	0.60	0.31; 1.14	0.13
	Age	0.98	0.53; 1.00	0.058	0.99	0.97; 1.01	**0.33**	**0.98**	**0.96; 1.00**	**0.03**	0.99	0.97; 1.01	0.40
	Female sex	**0.47**	**0.31; 0.71**	**<0.001**	**0.45**	**0.28; 0.72**	**<0.001**	**0.54**	**0.34; 0.84**	**0.01**	**0.50**	**0.29; 0.82**	**0.01**
	HLA-B27 negativity	**0.40**	**0.25; 0.64**	**<0.001**	**0.52**	**0.31; 0.87**	**0.02**	**0.40**	**0.22; 0.71**	**0.002**	**0.48**	**0.25; 0.89**	**0.02**
	Education vocational	**2.27**	**1.18; 4.62**	**0.02**	**2.59**	**1.28; 5.59**	**0.01**	**2.70**	**1.30; 6.08**	**0.01**	**2.86**	**1.31; 6.71**	**0.01**
	Education academic	**2.82**	**1.41; 5.95**	**0.01**	**3.23**	**1.52; 7.25**	**0.003**	**3.17**	**1.46; 7.40**	**0.01**	**3.30**	**1.44; 8.07**	**0.01**
	Body mass index				0.95	0.90; 1.00	0.06				**0.92**	**0.87; 0.98**	**0.02**
	Current smoking				0.82	0.51; 1.33	0.42				0.96	0.57; 1.58	0.86
	Elevated CRP				**3.22**	**2.06; 5.10**	**<0.001**				**3.04**	**1.87; 4.99**	**<0.001**
	Sacroiliitis on MRI				1.46	0.93; 2.31	0.11				1.44	0.87; 2.41	0.16
	(Number of patients/events)	(485/164)			(429/149)			(386/144)			(347/132)		

Response rates in patients with available outcome at 1 year (±6 months) and patients having discontinued the biologic in the meantime being considered non-responders. Significant results are shown in bold.
ASAS, Assessment in SpondyloArthritis international Society; ASAS40, 40% improvement according to the ASAS criteria; axSpA, axial spondyloarthritis; BASDAI50, 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein; HLA-B27, human leucocyte antigen-B27; TNFi, tumour necrosis factor inhibitor.

strictly required, and the presence of additional spondyloarthritis features was preferred but not mandatory. Presumably as a consequence of these specific inclusion criteria, only 38% of patients were of male sex, only 46% were HLA-B27 positive and only 35% had inflammatory sacroiliac MRI changes. These features stand in some contrast with our findings, showing a well-balanced sex distribution and considerably higher proportions of patients with HLA-B27 positivity and MRI sacroiliac inflammation (60% and 58%, respectively). Our patients' characteristics at inclusion in SCQM are more in line with findings from the French DESIR cohort,[19] which included patients with IBP of ≤3 years' duration in the context of overall symptoms suggestive of spondyloarthritis: male sex 46%, HLA-B27 positivity 57%. The proportion of patients with radiographical axSpA found in our patients with early axSpA (20%) was comparable with findings in cohorts of short IBP duration (20% in ESpAC and 26% in DESIR).[17 19] Inflammatory axial MRI changes were more prevalent in patients with early axSpA from the SCQM registry (58% for the sacroiliac joints and 31% for the spine) than in patients with IBP of short duration from the DESIR cohort (32% and 20%, respectively).[19] The higher inflammation load in patients in the SCQM registry might be explained by the fact that patients considered for bDMARD treatment are preferably recruited. The reason for this observation is the circumstance that, according to regulatory authorities, rheumatologists can deduct the costs of bDMARDs from their global treatment expenditures if the patients are followed in the clinical quality management programme that is at the core of SCQM.[20]

While the number of research questions to be evaluated in an early axSpA disease stage is substantial, the issue of a potential 'window of opportunity' for early treatment to allow for better outcomes remains at the forefront.[3 21]

Our multiple-adjusted retention and response analyses did not demonstrate better TNFi effectiveness in early versus established axSpA. The ASAS40 response rate found here in early axSpA (34%) is lower than in two prospective trials of infliximab in patients with symptom duration ≤3 years (60% and 75%, respectively).[22 23] These studies used, however, additional criteria to select their patients. The presence of inflammatory sacroiliac MRI changes was an absolute requirement for both studies, and all patients were additionally HLA-B27 positive in the first study,[22] while all patients were cotreated with an NSAID in the second study.[23] As both studies did not compare the treatment response in early versus established disease, the issue of additional criteria for adequate patient selection in early disease to be able to provide evidence for a window of opportunity in axSpA is still open. Comparison with these studies is further hampered by the observational nature of our analysis, which constrained us to measure the outcome at a rather late time point (1 year) and to consider patients who had discontinued the TNFi in the meantime as non-responders, regardless of the reason for discontinuation (response/tolerance analysis). Interestingly, our adjusted analyses did not identify the presence of sacroiliac joint inflammation as a predictor of better drug retention or treatment response. In contrast, HLA-B27 positivity was associated with treatment effectiveness here and is known to be an independent predictor of sacroiliac inflammation on MRI.[18] We have previously demonstrated that CRP and male sex seem to better describe the variability of treatment responses than HLA-B27 in individual patients.[24] An elevated CRP or a higher ASDAS was consistently associated with significantly better TNFi effectiveness in the analyses presented here. Indeed, CRP was shown to be the best predictor of good response in numerous prospective trials in both radiographical and non-radiographical disease and seems better than sacroiliac inflammation detected by MRI, as demonstrated in subgroup analyses.[25–29] Moreover, the amount and intensity of MRI inflammation might better predict response than the mere presence of sacroiliac bone marrow oedema.[30] Extensive sacroiliac bone marrow oedema is also a strong predictor of the development of structural lesions, in contrast to limited or intermediate inflammatory lesions.[31] Male sex was shown to be a predictor of future sacroiliac inflammation detected by MRI in patients with IBP of short duration.[18] It is also known to be a predictor of treatment response in both radiographical[32] and non-radiographical[33] axSpA and to be associated with accelerated radiographical progression at the levels of the sacroiliac joints[34] and the spine.[35] The impact of sex on treatment response seemed not to be different in early versus established axSpA, as demonstrated by the interaction analyses shown here.

Future analyses of treatment response and radiographical progression in early versus established disease are therefore warranted. Whether additional requirements on the amount of axial or systemic inflammation might help solve the conundrum of a window of opportunity in axSpA will potentially have to be investigated. As spinal radiographical progression is only minimal in the non-radiographical disease state,[36] an adequate length of the investigations might be crucial.

The prospective study design in one of the largest national axSpA cohorts treated under real-life conditions using validated assessments and the systematic collection of the start of axial symptoms in addition to the start of first symptoms represent its major strengths. The main analyses were performed on the whole population diagnosed as having axSpA. However, as the definition of early axSpA is intended to be used for research purposes only, we have presented data for the subgroup fulfilling the ASAS classification criteria[12] in parallel to further enhance the homogeneity of the study population.

As a major limitation of our analyses, MRIs were not collected systematically in SCQM to allow for the validation of the sacroiliac and spinal involvement indicated by the rheumatologist.[37 38] Additional limitations are related to the observational nature of our investigation and the fact that we might not have been able to adjust

for unknown remaining confounders. Recall bias with regard to the start of symptoms is a limitation inherent to the consensually chosen definition of early axSpA.[6] It is supposed to be more limited within a range of 2 years than with longer symptom duration.

In conclusion, 20% of patients with axSpA in this contemporary real-life axSpA cohort were included in an early disease stage according to the new consensus definition of early axSpA. While important patient characteristics are comparable in early and established axSpA, our results do not suggest better TNFi retention and better response rates in early axSpA in the context of a cut-off of 2 years of axial symptom duration as defined by ASAS. Comparable analyses in patients with shorter symptom duration might represent a next step for future analyses of early axSpA in suitable observational cohorts.

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Authors' contributions AC, AG and RM conceptualised and designed the study. AC, AR-R, BM, KB, MA, MJN, OD, PE, RB, RM and TH substantially contributed to the acquisition of clinical data. AG and AS processed the data and performed the statistical analyses. All authors contributed to the interpretation of the data. AC wrote the article, and all coauthors critically revised the manuscript for important intellectual content. AC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors agreed on the final content of the submitted manuscript.

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