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One-Third of European Patients with Axial Spondyloarthritis Reach Pain Remission With Routine Care Tumor Necrosis Factor Inhibitor Treatment

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ABSTRACT. ***Objective.*** To investigate the distribution of patient-reported outcomes (PROs) in patients with axial spondyloarthritis (axSpA) initiating a tumor necrosis factor inhibitor (TNFi), to assess the proportion reaching PRO "remission" across registries and treatment series, and to compare patients registered to fulfill the modified New York (mNY) criteria for ankylosing spondylitis (AS) vs patients with nonradiographic axSpA (nr-axSpA).

Methods. Fifteen European registries contributed PRO scores for pain, fatigue, patient global assessment (PtGA), Bath Ankylosing Spondylitis (AS) Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), and Health Assessment Questionnaire (HAQ) from 19,498 patients with axSpA. Changes in PROs and PRO remission rates (definitions: ≤ 20 mm for pain, fatigue, PtGA, BASDAI, and BASFI; ≤ 0.5 for HAQ) were calculated at 6, 12, and 24 months of treatment.

Results. Heterogeneity in baseline characteristics and outcomes between registries were observed. In pooled data, 6 months after the start of a first TNFi, pain score was reduced by approximately 60% (median at baseline/6/12/24 months: 65/25/20/20 mm) in patients on treatment. Similar patterns were observed for fatigue (68/32/30/25 mm), PtGA (66/29/21/20 mm), BASDAI (58/26/21/19 mm), BASFI (46/20/16/16 mm), and HAQ (0.8/0.4/0.2/0.2). Patients with AS (n = 3281) had a slightly better response than patients with nr-axSpA (n = 993). The Lund Efficacy Index (LUNDEX)-adjusted remission rates at 6 months for pain/fatigue/PtGA/BASDAI/BASFI/HAQ were 39%/30%/38%/34%/35%/48% for the AS cohort and 30%/21%/26%/24%/33%/47% for the nr-axSpA cohort. Better PRO responses were seen with a first TNFi compared to a second and third TNFi.

Conclusion. Patients with axSpA starting a TNFi achieved high PRO remission rates, most pronounced in those fulfilling the mNY criteria and for the first TNFi.

Key Indexing Terms: axial spondyloarthritis, patient-reported outcome measures, tumor necrosis factor inhibitors

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Axial spondyloarthritis (axSpA) is a chronic progressive inflammatory disease characterized by involvement of the axial skeleton and the sacroiliac joints. The onset of axSpA is usually before the age of 45 years and the burden of the disease includes back pain, reduced physical function, reduced mobility, fatigue, anxiety, and depression.[1,2] Consequently, and in the absence of effective treatment, patients may experience a reduced ability to work, limited social participation, and an overall lower quality of life.[3] Patients with the disease entity axSpA can be classified into those with radiographic axSpA (referred to as ankylosing spondylitis [AS]; ie, fulfilling the modified New York [mNY] criteria)[4] and those with nonradiographic axSpA (nr-axSpA). Patients with nr-axSpA are more frequently women and have less inflammation as measured by C-reactive protein (CRP) and magnetic resonance imaging compared to patients with AS.[5] However, the disease burden appears to be similar between patients with AS and patients with nr-axSpA.[5]

The goals of axSpA treatment are to reach clinical remission and to maintain physical function and ability to work.[6] Initial treatment comprises nonsteroidal antiinflammatory drugs (NSAIDs) combined with physical exercise. For patients with persisting disease activity despite NSAID treatment, treatment with a biological agent such as a tumor necrosis factor inhibitor (TNFi) is recommended.[6] Whether patients with AS and patients with nr-axSpA respond similarly to TNFi treatment in clinical practice is debated. Studies have shown shorter drug retention in patients with nr-axSpA[7] but similar response rates.[8]

Patient-reported outcomes (PROs) that measure pain, fatigue, and functional ability are central tools in the monitoring of axSpA symptoms and complement the clinical assessment.[9,10] No large real-world cohorts, including both patients with AS and nr-axSpA, have reported on PROs and PRO remission rates (ie, the proportion of patients achieving very low scores of PROs during TNFi treatment).

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The European Spondyloarthritis (EuroSpA) Research Collaboration Network was established in 2017 and is based on secondary use of data from 15 national quality registries collected in routine care. Based on data from EuroSpA, we aimed to investigate the effect of TNFi treatment on PROs and PRO remission rates in patients with axSpA across registries and treatment series, and to compare the patients with AS and those with nr-axSpA.

METHODS

The EuroSpA Research Collaboration Network. Fifteen registries contributed data, including (country, year of registry start): ATTRA (Czech Republic, 2002), DANBIO (Denmark, 2000), National Register of Biological Treatment in Finland (ROB-FIN; Finland, 1999), Icelandic Nationwide Database of Biologic Therapy (ICEBIO; Iceland, 2007), Italian Group for the Study of Early Arthritis (GISEA; Italy, 2008), Amsterdam Rheumatology and Immunology Center (ARC; Netherlands, 2005), Norwegian Disease-Modifying Antirheumatic Drugs Register (NOR-DMARD; Norway, 2000), Rheumatic Diseases Portuguese Register (Reuma.pt; Portugal, 2008), the Romanian Registry of Rheumatic Diseases (RRBR; Romania, 2015), Biorx.si (Slovenia, 2008), Spanish Registry for Adverse Events of Biological Therapy in Rheumatic Diseases (BIOBADASER; Spain, 2000), Antirheumatic Therapy in Sweden (ARTIS; Sweden, 1999), Swiss Clinical Quality Management in Rheumatic Diseases (SCQM; Switzerland, 2006), TURKBIO (Turkey, 2011), and British Society for Rheumatology Biologics Register in AS (BSRBR-AS; United Kingdom, 2012).[11,12,21-24,13-20] Based on a prespecified variable list, anonymized datasets were created and uploaded securely; data were subsequently harmonized to a common standard. After pooling, composite scores and classification criteria were calculated.

Study population. Inclusion criteria in the present study were an axSpA diagnosis at age ≥ 18 years, initiation of TNFi as the first biological treatment in the period January 1, 2009, to December 31, 2018, and at least 1 visit (at baseline, 6, 12, or 24 months) with any registered PRO while being treated with a TNFi. Patients who switched from a first to a second TNFi and from a second to a third TNFi, without non-TNFi biologic or targeted synthetic disease-modifying antirheumatic drug treatment in between, were also included in the analyses of second TNFi and third TNFi, respectively. Patients with available information on classification criteria were classified as (1) fulfilling the mNY criteria for AS (AS cohort), or (2) fulfilling the Assessment of SpondyloArthritis international Society (ASAS) criteria but not the mNY criteria (nr-axSpA cohort). Data collection ended on November 4, 2019, which allowed all patients to have a minimum of 10 months of follow-up (the latest start of first TNFi treatment was December 31, 2018). Start of follow-up was defined as the date of first, second, or third TNFi treatment start, and end of follow-up was defined as the end of first, second, or third TNFi treatment, end of registry capture, or death, whichever came first.

Data collected. Variables collected at the start of each TNFi treatment were age, years since diagnosis, sex, classification criteria (mNY and ASAS), BMI (calculated as weight in kilograms divided by height in meters squared), current smoking status, HLA-B27 status, name of TNFi treatment, physician global assessment (PGA), CRP, erythrocyte sedimentation rate (in mm/h), AS Disease Activity Score (ASDAS), and Bath AS Metrology Index (BASMI).[25] The following PROs were collected at the start of each TNFi treatment and at 6, 12, and 24 months of follow-up: patient's assessment of total pain (pain), patient's assessment of fatigue (fatigue), patient's global assessment of disease activity (PtGA), Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), and the Health Assessment Questionnaire (HAQ).[26-30] The PROs (including BASDAI and BASFI) were registered on a 0 mm to 100 mm visual analog scale (VAS) in most registries, except for HAQ, which was scored on a scale ranging from 0 to 3. Three registries (RRBR, Biorx.si, and SCQM) used a 0 to 10 numeric rating scale (NRS) for pain, fatigue, PtGA, and PGA; these scores were multiplied by 10 to allow comparison with VAS scores. The visits at 6, 12, and 24 months were defined as available visits in the periods of 90 to 270 days, 271 to 545 days, and 546 to 910 days, respectively, after the start of first, second, or third TNFi treatment in patients who continued treatment. Priority was given to visits closest in time to 180, 365, and 730 days, respectively. Medians for PROs are only reported in tables and figures if ≥ 50 patients in the cohort had available data.

PRO remission. There is no international consensus on cut-off values for PRO remission in patients with axSpA. However, in a previous study, partial PRO remission was defined as pain < 20 mm, PtGA < 20 mm, and BASFI < 20 mm.[31] Based on this, we defined PRO remission in the present study as scores ≤ 20 mm for pain, fatigue, PtGA, BASDAI, and BASFI, and as HAQ scores ≤ 0.5.[4,31] Both crude and Lund Efficacy Index (LUNDEX)-adjusted[32] PRO remission rates were calculated. The LUNDEX adjustment multiplies the crude remission rate with the fraction of patients still receiving treatment at the timepoint of interest, thus taking drug retention into account.

Ethics. All participating registries obtained the necessary approvals in accordance with legal, compliance, and regulatory requirements from national data protection agencies and/or research ethics boards prior to the data transfer to the EuroSpA coordinating center. This publication follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines[33] and the Declaration of Helsinki.

Primary and secondary outcomes. The primary outcome was the distribution of pain scores at 6 months of TNFi treatment. Secondary outcomes were the pain score distribution at 12 and 24 months, and the distribution of fatigue, PtGA, BASDAI, BASFI, and HAQ scores at 6, 12, and 24 months. Secondary outcomes included assessment of the fraction of patients with axSpA in PRO remission (as defined above) after 6, 12, and 24 months, changes in PROs from baseline to 6, 12, and 24 months, and concordance of remission across PROs in individual patients.

Statistical analyses. We followed the predefined study protocol and the statistical analysis plan. Descriptive statistics (medians with IQRs) were applied. Primary analyses were performed on observed data with no imputation of missing data. No statistical comparisons were performed. As sensitivity analyses, the last observation was carried forward (LOCF) for the 12- and 24-months analyses of continuous measures. All statistical analyses were performed in R version 3.6.1 (R Foundation).

RESULTS

Patients. We included data on 19,498 biologic-naïve patients with axSpA who constituted the pooled cohort (All) for the main analyses. Among these, 3281 patients were registered to fulfill the mNY criteria (AS cohort) and 993 were registered to fulfill the ASAS criteria for axSpA and to not fulfill the mNY criteria (nr-axSpA cohort; Supplementary Figure S1, available with the online version of this article). Classification criteria were available in 10 of the 15 registries (Supplementary Table S1).

In the pooled cohort, adalimumab (ADA) was the most frequently prescribed first TNFi (32%), followed by etanercept (ETN; 24%), infliximab (IFX; 22%), golimumab (GOL; 16%), and certolizumab pegol (CZP; 6%). Large differences in choice of first TNFi were observed across registries (Supplementary Table S2, available with the online version of this article). Choice of TNFi were comparable for the second and third TNFi (ADA at 29%/26%, ETN at 32%/23%, IFX at 13%/16%, GOL at 17%/21%, and CZP at 9%/13%) in the pooled cohorts and in the 2 subcohorts (Table).

Table. Baseline characteristics of 19,498 patients with axSpA at start of first TNFi treatment.

	Started First TNFi Treatment Between January 1, 2009, to December 31, 2018[a]					
	All, N = 19,498		AS Cohort, n = 3281[b]		nr-axSpA Cohort, n = 993[c]	
	Patients With Available Data, n (%)	Median (IQR) or n (%)	Patients With Available Data, n (%)	Median (IQR) or n (%)	Patients With Available Data, n (%)	Median (IQR) or n (%)
Age at TNFi start, yrs	19,498 (100)	41 (33-51)	3281 (100)	44 (35-54)	993 (100)	40 (32-49)
Age at diagnosis, yrs	16,251 (83)	35 (27-44)	3200 (98)	35 (28-45)	981 (99)	36 (28-45)
Yrs since diagnosis	16,251 (83)	2 (0-8)	3200 (98)	4 (1-11)	981 (99)	1 (0-4)
Men	19,498 (100)	11,401 (58)	3281 (100)	2182 (67)	993 (100)	475 (48)
BMI, kg/m^2	8824 (45)	26 (23-29)	2451 (75)	26 (23-30)	706 (71)	25 (23-29)
Current smokers	16,801 (86)	4033 (24)	3027 (92)	885 (29)	951 (96)	276 (29)
HLA-B27 positive	8781 (45)	6556 (75)	2701 (82)	1854 (69)	890 (90)	620 (70)
First TNFi drug (EMA approval)	19,498 (100)		3281 (100)		993 (100)	
IFX (1999)		4307 (22)		542 (17)		133 (13)
ETN (2000)		4659 (24)		738 (22)		184 (18)
ADA (2003)		6278 (32)		1313 (40)		392 (39)
CZP (2009)		1167 (6)		108 (3)		42 (4)
GOL (2009)		3087 (16)		580 (18)		242 (24)
First TNFi start, yr	19,498 (100)		3281 (100)		993 (100)	
2009-2014		10,430 (53)		1711 (52)		581 (58)
2015-2018		9068 (47)		1570 (48)		412 (42)
PROs[d]						
Pain, mm	12,641 (65)	65 (45-80)	1718 (52)	70 (50-80)	660 (66)	70 (50-80)
Fatigue, mm	9403 (48)	68 (47-80)	1120 (34)	70 (52-81)	593 (60)	71 (53-83)
PtGA, mm	13,059 (67)	66 (48-80)	1842 (56)	70 (50-81)	716 (72)	71 (57-83)
BASDAI, mm	12,641 (63)	58 (42-72)	2066 (63)	63 (49-76)	655 (66)	64 (49-76)
BASFI, mm	10,095 (52)	46 (25-66)	1898 (58)	55 (35-73)	619 (62)	49 (29-68)
HAQ	9561 (49)	0.8 (0.5-1.2)	760 (23)	0.9 (0.5-1.4)	209 (21)	0.9 (0.5-1.4)
Physician-reported outcomes						
PGA, mm	7988 (41)	41 (23-60)	1046 (32)	50 (30-68)	478 (48)	45 (30-60)
Blood tests						
CRP, mg/L	13,154 (67)	8 (3-20)	2112 (64)	10 (3-23)	698 (70)	6 (2-17)
ESR, mm/h	10,547 (54)	18 (8-33)	1592 (49)	23 (10-40)	329 (33)	13 (6-31)
Composite indexes						
ASDAS	8928 (46)	3.5 (2.8-4.1)	1546 (47)	3.7 (3.1-4.4)	560 (56)	3.5 (3.0-4.1)
BASMI	3299 (17)	2.9 (1.4-4.0)	956 (29)	3.0 (2.0-5.0)	374 (38)	2.0 (1.0-3.3)

[a] By 2009, all relevant TNFi drugs were on the market and the patients included in this cohort had the same treatment options as patients treated today. However, after 2009, other biologic treatment options, which can replace TNFi drugs, have been marketed. [b] Patients registered as fulfilling the mNY criteria for AS, initiating treatment after 2009. [c] Patients registered to fulfill the ASAS criteria for axSpA and to not fulfill the mNY criteria for AS (nr-axSpA), initiating treatment after 2009. [d] Pain, fatigue, PtGA, BASDAI, BASFI, and PGA were scored on a 0-100 mm VAS; HAQ was scored on a scale ranging from 0-3. Three registries (RRBR, Biorx.si, and SCQM) used a 0-10 NRS for pain, fatigue, PtGA, and PGA. ADA: adalimumab; AS: ankylosing spondylitis; 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; CZP: certolizumab pegol; EMA: European Medicines Agency; ESR: erythrocyte sedimentation rate; ETN: etanercept; GOL: golimumab; HAQ: Health Assessment Questionnaire; IFX: infliximab; mNY: modified New York criteria; nr-axSpA: nonradiographic axSpA; NRS: numerical rating scale; PGA: physician global assessment; PRO: patient-reported outcome; PtGA: patient global assessment of disease activity; RRBR: Romanian Registry of Rheumatic Diseases; SCQN: Swiss Clinical Quality Management in Rheumatic Diseases; TNFi: tumor necrosis factor inhibitor; VAS: visual analog scale.

Baseline characteristics and PROs. The Table shows that at baseline, the pooled cohort had considerable disease activity as assessed by composite scores and PROs.

Patients starting a first TNFi in each of the 15 registries differed considerably with regard to demographic characteristics, disease activity levels, and baseline PROs (Supplementary Table S1, available with the online version of this article). The median age at the start of TNFi treatment varied from 38 years in the TURKBIO registry to 48 years in the ARC registry. PRO scores at the start of the first TNFi varied between registries. The registries with the lowest/highest median scores were NOR-DMARD/RRBR for pain (49/90 mm), NOR-DMARD/RRBR and BSRBR-AS for fatigue (50/80 mm), ROB-FIN/RRBR (50/80 mm) for PtGA, ROB-FIN/RRBR for BASDAI (42/74 mm), ROB-FIN/BSRBR-AS for BASFI (28/66 mm), and NOR-DMARD/RRBR for HAQ (0.5/1.9).

Figure 1 demonstrates that the baseline PROs were comparable in the pooled cohort (All) at initiation of the first,

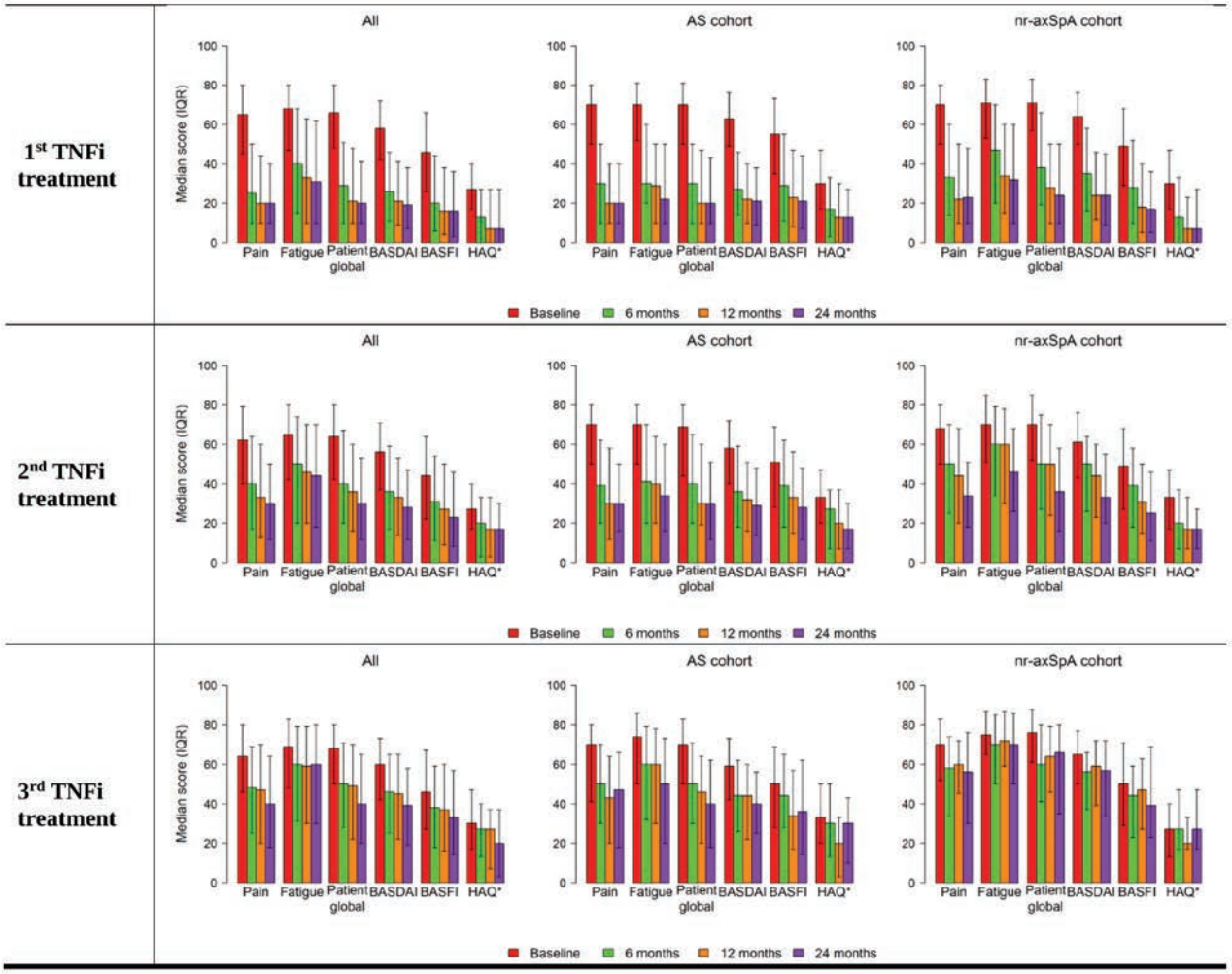


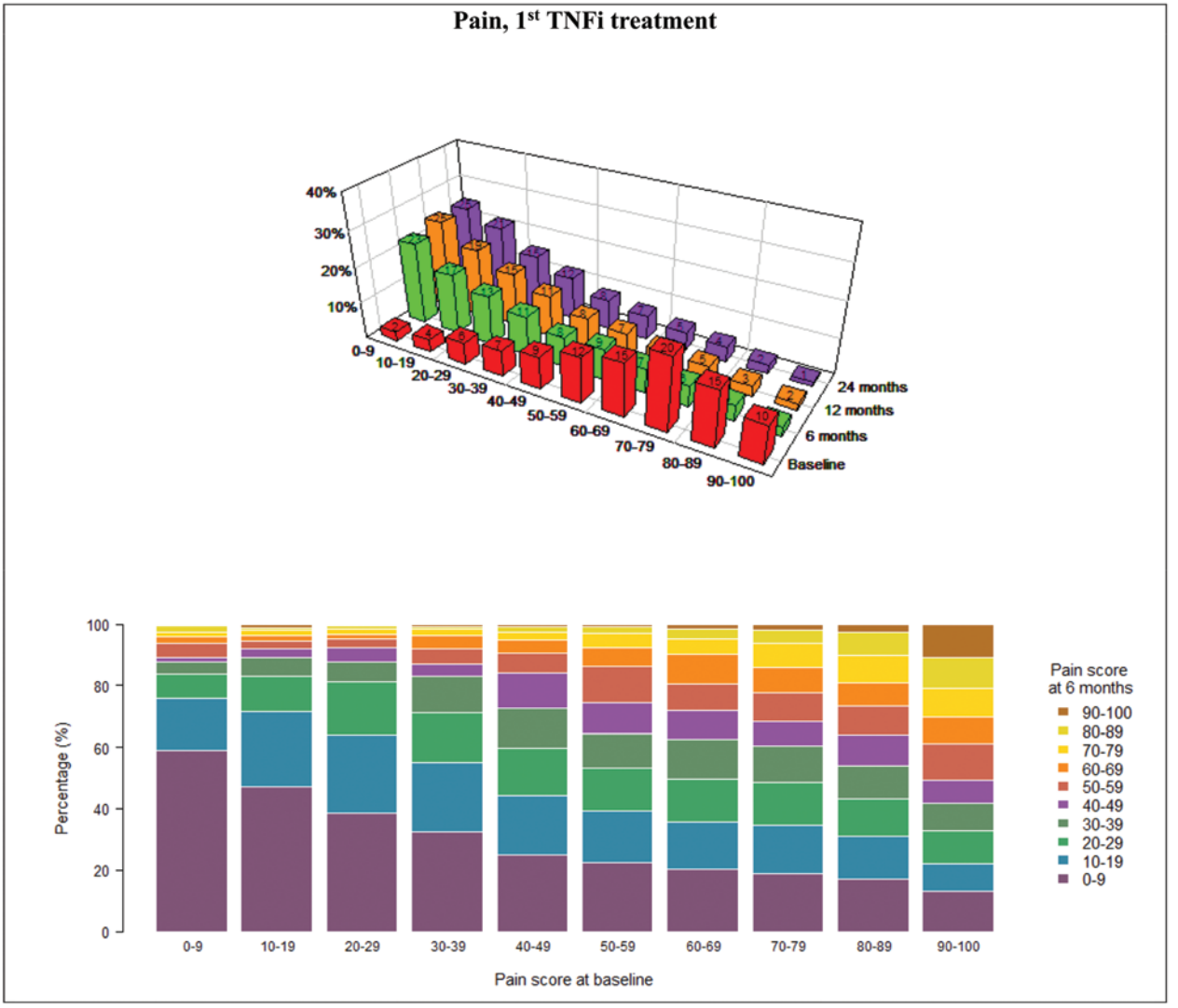
Figure 1. Median PRO scores for the pooled cohort and for the 2 subcohorts for first, second, and third TNFi treatment at 6, 12, and 24 months after initiation of first TNFi treatment. Patients with AS met the mNY criteria for classification. * HAQ was scored on a scale ranging from 0 to 3 and converted to 0-100 for the bar chart. AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; HAQ: Health Assessment Questionnaire; mNY: modified New York; nr-axSpA: nonradiographic axial spondyloarthritis; Patient global: patient global assessment of disease activity; PRO: patient-reported outcome; TNFi: tumor necrosis factor inhibitor.

second, and third TNFi, which was also the case for ASDAS (3.5/3.2/3.3). The AS and nr-axSpA cohorts had similar PRO scores at the start of first TNFi treatment: 70/70 for pain, 70/71 for fatigue, 70/71 for PtGA, 63/64 for BASDAI, 55/49 for BASFI, and 0.9/0.9 for HAQ (Table). Values for PGA, blood tests, and composite indexes were also comparable across the 2 subcohorts.

PROs after 6, 12, and 24 months of treatment. Figure 2 (upper panel) shows that after 6 months of a first TNFi, pain scores in the pooled cohort had improved compared to baseline measures and that scores at 12 and 24 months of treatment were comparable to those at 6 months. Similar patterns were seen for fatigue, PtGA, BASDAI, BASFI, and HAQ (Supplementary Figure S2A-E, available with the online version of this article). Figure 2 (lower panel) shows the distribution of patients according to pain scores at 6 months and pain scores at baseline. Among patients who reported very high pain scores (defined as 80-89 mm and 90-100 mm) at baseline, 17% and 13%, respectively, reported very low pain scores (defined as ≤ 9 mm) after 6 months of treatment (Figure 1). In contrast, 25% and 32% of patients reporting moderate pain scores at baseline (defined as 40-49 mm and 30-39 mm) achieved a very low pain score after 6 months of treatment. Similarly, 6%/13%/8%/5%/3% of patients who reported very high fatigue/PtGA/BASDAI/BASFI/HAQ scores at baseline reported very low scores after 6 months of treatment (Supplementary Figure S2A-E).

In all registries, PROs decreased during TNFi treatment (Supplementary Figure S3, available with the online version of this article), whereas the absolute values varied considerably. As an example, the highest median pain score after 6 months of a first TNFi was found in GISEA (40 mm) and the lowest in ICEBIO (14 mm).

Large differences in PROs at 6, 12, and 24 months in patients from the pooled cohort treated with a first, second, and third TNFi, respectively, were observed (Figures 3 and 4; Supplementary Tables S2A-C, available with the online version



Pain score at 6 months

Pain score at baseline	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-100
0-9	115 (59%)	33 (17%)	15 (8%)	8 (4%)	3 (2%)	9 (5%)	4 (2%)	3 (2%)	4 (2%)	1 (1%)
10-19	141 (47%)	71 (24%)	34 (11%)	19 (6%)	8 (3%)	8 (3%)	5 (2%)	5 (2%)	3 (1%)	3 (1%)
20-29	204 (39%)	133 (25%)	90 (17%)	33 (6%)	25 (5%)	15 (3%)	8 (2%)	8 (2%)	6 (1%)	3 (1%)
30-39	196 (32%)	137 (23%)	99 (16%)	73 (12%)	24 (4%)	31 (5%)	26 (4%)	12 (2%)	6 (1%)	4 (1%)
40-49	194 (25%)	151 (19%)	122 (16%)	99 (13%)	89 (11%)	52 (7%)	34 (4%)	19 (2%)	14 (2%)	6 (1%)
50-59	235 (22%)	177 (17%)	145 (14%)	118 (11%)	104 (10%)	123 (12%)	65 (6%)	49 (5%)	25 (2%)	7 (1%)
60-69	255 (20%)	199 (16%)	178 (14%)	161 (13%)	117 (9%)	112 (9%)	123 (10%)	65 (5%)	39 (3%)	20 (2%)
70-79	325 (19%)	279 (16%)	240 (14%)	204 (12%)	140 (8%)	157 (9%)	146 (8%)	134 (8%)	78 (4%)	32 (2%)
80-89	226 (17%)	184 (14%)	163 (12%)	139 (10%)	133 (10%)	126 (9%)	100 (8%)	122 (9%)	101 (8%)	34 (3%)
90-100	112 (13%)	80 (9%)	94 (11%)	76 (9%)	67 (8%)	99 (11%)	77 (9%)	79 (9%)	89 (10%)	94 (11%)

Figure 2. Pain scores during first TNFi treatment. Upper panel: 3-D bar chart of the relative frequency (y-axis) of pain scores (mm given on x-axis) at baseline and after 6, 12, and 24 months of first TNFi treatment, respectively (z-axis). Lower panel: Stacked bar chart showing the distribution of pain scores of patients with axSpA after 6 months of treatment dependent on how the same patients scored at start of TNFi treatment (baseline). Table: n (%) of patients as illustrated in stacked bar chart. axSpA: axial spondyloarthritis; TNFi: tumor necrosis factor inhibitor.

of this article), with achievement of lower PROs at 6, 12, and 24 months of treatment and larger changes from baseline during the first treatment compared to the second and third. The change in PROs from baseline to 6, 12, and 24 months presented in Figure 4 should be interpreted together with the corresponding retention rates (85%/75%/65% for first TNFi,

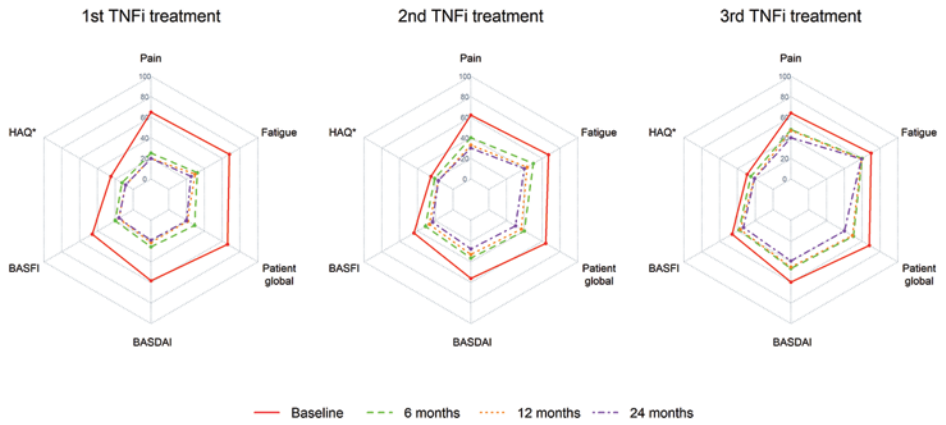


Figure 3. Radar charts showing PRO scores of patients with axSpA at the start of TNFi treatment (baseline) and at 6, 12, and 24 months after initiation of treatment with first TNFi (baseline, n = 19,498), second TNFi (baseline, n = 6304), and third TNFi (baseline, n = 1927). * HAQ was scored on a scale ranging from 0-3 and converted to a 0-100 scale for the radar chart. In NOR-DMARD a modified version of HAQ was used. axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; HAQ: Health Assessment Questionnaire; NOR-DMARD: Norwegian Disease-Modifying Antirheumatic Drugs Register; Patient global: patient global assessment of disease activity; PRO: patient-reported outcome; TNFi: tumor necrosis factor inhibitor.

78%/66%/56% for second TNFi, and 76%/63%/50% for third TNFi).

The same trend across treatment series was also found in the AS and nr-axSpA cohorts (Figure 4; Supplementary Tables S2A-C, available with the online version of this article). In addition, the AS cohort generally achieved lower absolute PROs during therapy and experienced larger changes from baseline. The 12-month retention rate for the AS cohort was 81% (95% CI 80-83; first TNFi), whereas the corresponding rate in the nr-axSpA cohort was 69% (95% CI 67-72).

Sensitivity analyses applying LOCF to missing continuous PROs only affected the measures at 12 and 24 months marginally for first, second, and third TNFi (Supplementary Table S4, available with the online version of this article).

PRO remission 6, 12, and 24 months after start of first TNFi treatment. After 6 months of first TNFi treatment, the crude pain remission rate was 46% in the pooled cohort. Taking drug retention at 6 months into account, the LUNDEX-adjusted remission rate for pain was 39%. After 12 and 24 months of treatment, the LUNDEX-adjusted remission rates for pain were 37% and 32%, respectively (Figure 5; Supplementary Table S2A, available with the online version of this article).

As for the PROs, LUNDEX-adjusted PRO remission rates also differed markedly across registries (data not shown).

Similarly, the LUNDEX-adjusted PRO remission rates were higher after 6 months of the first TNFi treatment compared to the second and third TNFi (Supplementary Figure S4 and Table S2A-C, available with the online version of this article).

The AS cohort achieved higher LUNDEX-adjusted remission rates for all PROs than the nr-axSpA cohort (Figure 5; Supplementary Table S2A-C, available with the online version of this article).

Concordance of remission across PROs in individual patients. In a subset of patients treated with a first TNFi who had available 6 months' assessments for all 6 PROs (n = 3322), 27% were in remission in all 6 PROs at 6 months, whereas 73% had achieved remission in at least 1 PRO. Corresponding percentages for remission in 2, 3, 4, and 5 PROs were 63%, 52%, 43%, and 37%.

In Supplementary Table S3 (available with the online version of this article), the concordance between remission across the 6 PROs are shown, demonstrating that patients having achieved pain remission are likely to be in remission across several PROs, whereas remission in the functional measures HAQ and BASFI are less concordant with other PROs.

DISCUSSION

In the present study of patients with axSpA from 15 European countries, we report, for the first time to our knowledge, PRO remission rates in a large real-world cohort. The disease burden at baseline as assessed by 6 PRO measures was high. Across the 15 registries, PROs at baseline varied markedly; however, in all registries TNFi treatment resulted in improvements of PROs.

Overall, 6 months after the start of a first TNFi, the disease burden as experienced by patients had been markedly reduced (approximately 60%), and a third of patients were in a state of PRO remission regarding at least 1 PRO (ie, a score ≤ 20 mm). Despite an increasing focus on PROs for the monitoring of patients with axSpA, PRO remission rates have not previously been reported, to our knowledge, in a real-world setting. Since there is no international consensus on cut-off values for PRO remission, we based our cut-off values on a previous study[31] defining remission as scores of < 20 (on a 0-100 mm scale) for pain, PtGA, and BASFI, and used similar values for PROs with no recommendations reported in the literature (BASDAI, fatigue). As several registries assess PROs on a 0 to 10 NRS, we chose to apply a cut-off for remission of ≤ 20. An important

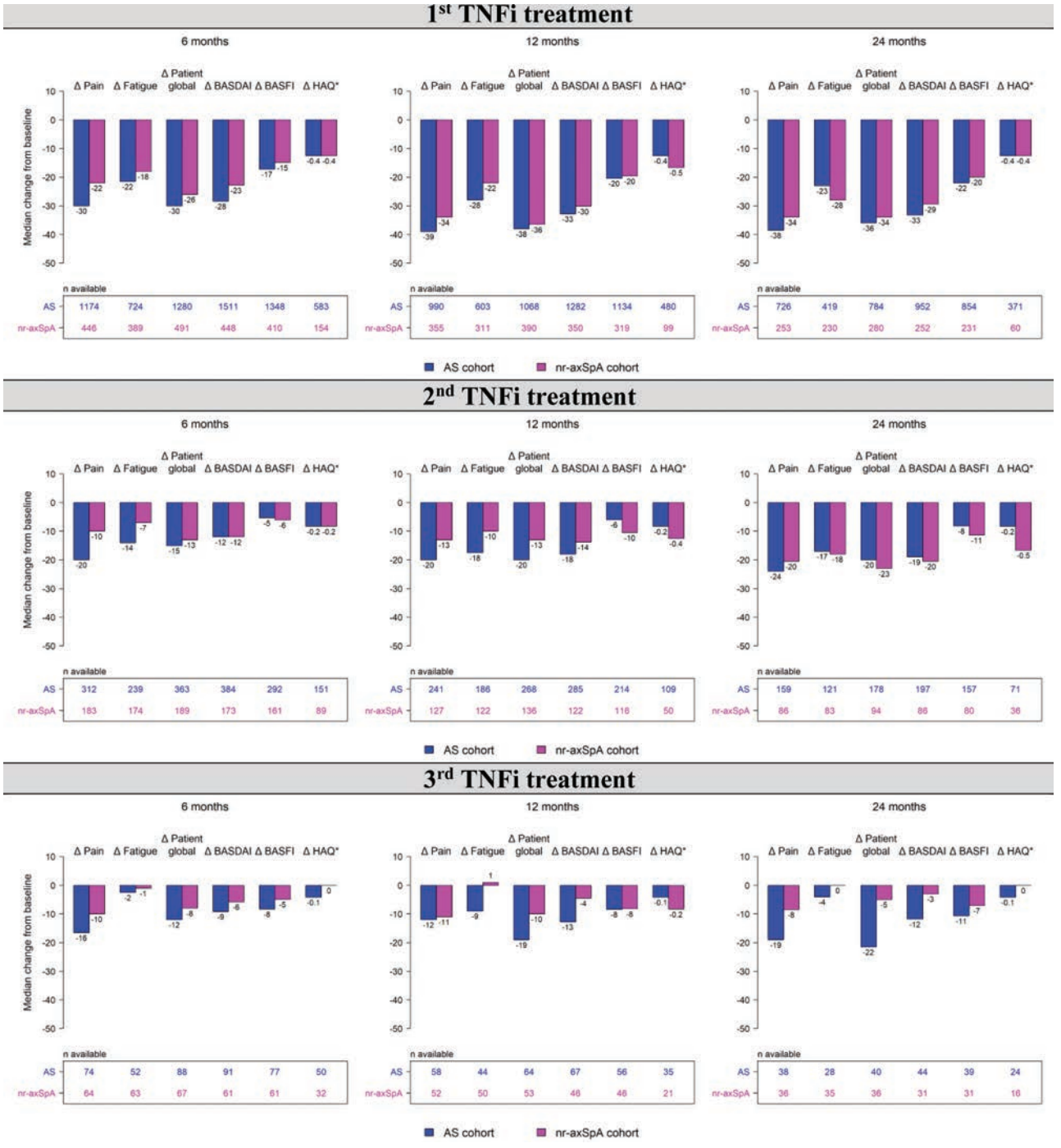


Figure 4. Changes in PROs from baseline to 6, 12, and 24 months after the start of first, second, and third TNFi treatment in the AS cohort and the nr-axSpA cohort (data as observed). The AS cohort were patients registered to fulfill the mNY criteria for AS. The nx-axSpA cohort were patients registered to fulfill the ASAS criteria for axSpA and to not fulfill the mNY criteria for AS. Patients with AS were registered to fulfill the mNY criteria. * HAQ was scored on a scale ranging from 0-3. In NOR-DMARD, a modified version of HAQ (mHAQ) was used. AS: ankylosing spondylitis; ASAS: Assessment of SpondyloArthritis international Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; HAQ: Health Assessment Questionnaire; mNY: modified New York; NOR-DMARD: Norwegian Disease-Modifying Antirheumatic Drugs Register; nr-axSpA: nonradiographic axial spondyloarthritis; Patient global: patient global assessment of disease activity; PRO: patient-reported outcome; TNFi: tumor necrosis factor inhibitor.

finding was that the high remission rates observed after 6 months were largely similar to the rates observed up to 24 months when adjusting (LUNDEX) for patients who withdrew from treatment during follow-up. Thus, after 6 months' treatment, no additional benefit can be expected at the group level. This was seen across individual registries and all TNFi treatment series.

The effect of TNFi treatment on PROs has been investigated in several randomized controlled trials (RCTs) of either AS or

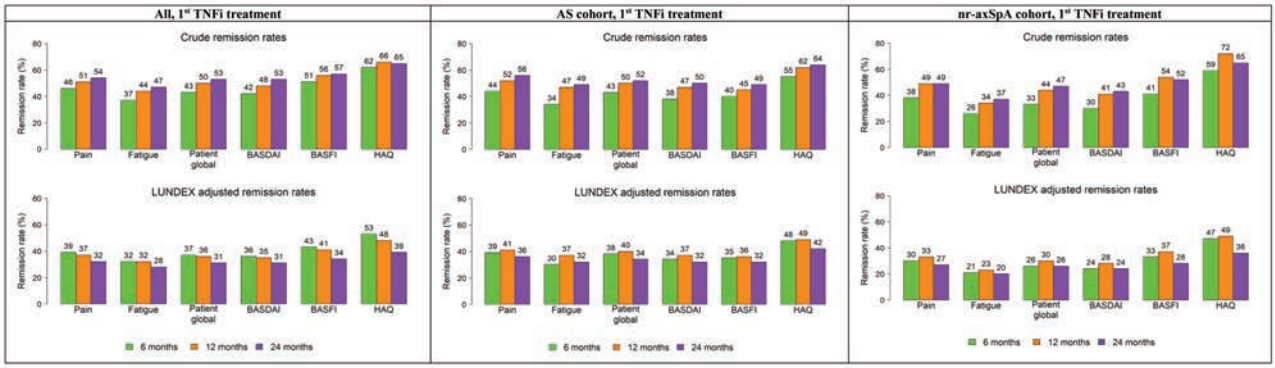


Figure 5. PRO remission rates (%) 6, 12, and 24 months after the start of first TNFi treatment for the full cohort and the 2 subcohorts. Definitions of remission: scores ≤ 20 mm for pain, fatigue, patient global, BASDAI, and BASFI, and HAQ scores ≤ 0.5. Upper panels: crude remission rates. Lower panels: LUNDEX-adjusted remission rates.[41] In NOR-DMARD, a modified version of HAQ (mHAQ) was used. AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; HAQ: Health Assessment Questionnaire; LUNDEX: Lund Efficacy Index; mNY: modified New York criteria; NOR-DMARD: Norwegian Disease-Modifying Antirheumatic Drugs Register; nr-axSpA: nonradiographic axial spondyloarthritis; Patient global: patient global assessment of disease activity; PRO: patient-reported outcome; TNFi: tumor necrosis factor inhibitor.

nr-axSpA cohorts[27,34-36] and in smaller real-world cohorts,[37,38] all reporting beneficial effects. However, it has been questioned whether these effects can be generalized to real-world patients.[39] Our large study provides real-world evidence that in routine care, substantial improvement in PROs can be expected after initiation of TNFi treatment,[38,40-42] which is in agreement with previous, smaller real-world studies.

When looking into changes in individual patients over time, we found that in the patients with very high pain scores (≥ 90 mm) at baseline only 22% achieved pain remission. In contrast, in patients with moderate pain score (40-49 mm) at TNFi start, 44% achieved pain remission. An association between extreme PRO and poorer treatment response has also been reported by Krabbe et al, where it was hypothesized to be caused by comorbid conditions such as chronic pain syndrome.[43]

We were able to study subcohorts of patients with AS according to the mNY criteria and patients with nr-axSpA. A challenge with the subcohorts is that the classification of patients was performed at enrollment in the registries, typically at the start of a first TNFi. Thus, a subset of patients in the nr-axSpA cohort may have progressed to AS when they received the second and third TNFi. Patients in the AS cohort had slightly higher TNFi treatment response and PRO remission rates than patients in the nr-axSpA cohort. This finding might be explained by a higher degree of uncertainty of the nr-axSpA diagnosis (ie, some patients may have been misclassified). In a recent study from the EuroSpA collaboration, the 12-month TNFi retention rate was higher in the AS cohort (83%) than in the nr-axSpA cohort (73%); a finding replicated in the present study based on data from the same registries.[44] In our study, the percentage of men was 67% in the AS cohort and 48% in the nr-axSpA cohort. The higher percentage of women in the nr-axSpA cohort may have contributed to a poorer PRO response after TNFi treatment, as previous studies have shown poorer response to TNFi in women compared to men.[45,46] These findings are further supported by a study based on pooled data from 4 RCTs including 1263 patients with AS, which showed that men had a better response to ETN than women.[47]

A major strength of the present study is the inclusion of more than 19,000 patients with axSpA treated with TNFi in routine care across 15 European countries. The extensive collection of PROs in the included registries allowed us to draw a detailed picture of the evolution of PROs at different timepoints after TNFi treatment start, to describe differences in proportions of patients reaching PRO remission, and to explore differences in PRO measures across registries, treatment series, and diagnostic subcohorts, though the number of patients that could be included in the analyses differed across PRO and follow-up visit. The information gathered by the PROs gives a unique understanding of the patients' perspective, which may improve treatment of patients with axSpA in routine care.[9,48] We hypothesize that the observed heterogeneity in patient characteristics and treatment outcomes between registries arise from several sources. First, differences in treatment accessibility between countries will affect the demographic and baseline characteristics of registry populations. Second, organizational differences in inclusion criteria, registry coverage, and follow-up schedule between registries may affect the observed outcomes.

Unfortunately, information on country-specific guidelines and recommendations for TNFi treatment of patients with axSpA was not available in the present study. Also, differences in the wording of the PRO questions may have contributed to the observed variation, which could be investigated further in future studies. Thus, the differences in PROs between registries should be interpreted with caution.

One limitation of the present study is the lack of information on comorbidities such as fibromyalgia and osteoporosis; thus, we were unable to adjust for their potential effects on PROs.[49] The inherent limitation of missing data in registry research should also be mentioned. For the present study, missing data on classification criteria had a large effect on the number of patients in the AS and nr-axSpA cohorts, with consequences for the generalizability of the results, as only 10 of the 15 registries provided data on classification criteria. Further, patients with a good response to TNFi treatment might be overrepresented in our study as

a result of a higher motivation to comply with their physician appointments, leading to higher data availability. In the pooled cohort, only 44% of patients still treated with their first TNFi after 12 months had a pain assessment, and if these patients were compliant with their hospital visit due to a good response, a potential bias toward lower PROs may have been introduced. However, a bias in the opposite direction could also have been introduced, as patients with high disease activity in need of treatment intensification are more likely to have a hospital visit scheduled.

In conclusion, this large study of real-world patients with axSpA showed heterogeneity in baseline characteristics and PROs between registries, and clear effects of TNFi treatment across registries, diagnostic subcohorts, and treatment series. The highest PRO remission rates were seen in those fulfilling the mNY criteria and patients treated with their first TNFi.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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