One-third of European axial spondyloarthritis patients reach pain "remission" with routine care TNF-inhibitor treatment

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ABSTRACT

Objectives: To investigate the distribution of patient-reported outcomes (PROs) in axial spondyloarthritis (axSpA) patients 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 New York criteria for ankylosing spondylitis (AS) versus non-radiographic axSpA (nr-axSpA) patients.

Methods: Fifteen European registries contributed PRO scores for pain, fatigue, patient global, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Health Assessment Questionnaire (HAQ) from 19,498 axSpA patients. Changes in PROs and PRO "remission" rates (definitions: ≤20 mm for pain, fatigue, patient global, 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, six months after start of a 1st 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), patient global (66/29/21/20), BASDAI (58/26/21/19), BASFI (46/20/16/16) and HAQ (0.8/0.4/0.2/0.2). Patients with AS, n=3281 had a slightly better response than nr-axSpA patients, n=993. LUNDEX-adjusted "remission" rates at 6 months for pain/fatigue/patient global/BASDAI/BASFI/HAQ were 39%/30%/38%/34%/35%/48% for the AS cohort and 30%/21%/26%/24%/33%/47% for the non-radiographic axSpA cohort. Better PRO responses were seen with a 1st TNFi compared to 2nd and 3rd TNFi.

Conclusions: AxSpA patients starting a TNFi achieved high PRO "remission" rates, most pronounced in those fulfilling the modified New York criteria and for the first TNFi.

INTRODUCTION

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 reduced ability to work, limited social participation and an overall lowered quality of life.(3) Patients with the disease entity axSpA can be classified into those with radiographic axSpA (ankylosing spondylitis (AS)), i.e. fulfilling the modified New York criteria(4) and those with non-radiographic axSpA (nr-axSpA). Patients with nr-axSpA are more frequently women and have less inflammation as measured by C-reactive protein and MRI compared to AS patients(5). However, the disease burden appears to be similar between AS and nr-axSpA patients.(5)

The goals of axSpA treatment are to reach clinical remission and to maintain physical function and ability to work.(6) Initial treatment comprises non-steroidal anti-inflammatory drugs (NSAIDs) combined with physical exercise. For patients with persisting disease activity despite NSAID treatment, treatment with a biological agent such as tumor necrosis factor-alpha inhibitors (TNFi) is recommended.(6) Whether patients with AS and nr-axSpA respond similarly to TNFi treatment in clinical practice is debated. Studies have shown shorter drug retention in nr-axSpA patients,(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 AS and nr-axSpA patients, have reported on PROs and PRO

"remission" rates, ie the proportion of patients achieving very low scores of PROs during TNFi treatment.

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 impact of TNFi treatment on PROs and PRO "remission" rates in axSpA patients across registries and treatment series, and to compare the AS and nr-axSpA patients.

METHODS

The EuroSpA Research Collaboration Network

Fifteen registries contributed data (country; year of registry start): ATTRA (Czech Republic; 2002), DANBIO (Denmark; 2000), ROB-FIN (Finland; 1999), ICEBIO (Iceland; 2007), GISEA (Italy; 2008), ARC (Netherlands; 2005), NOR-DMARD (Norway; 2000), Reuma.pt (Portugal; 2008), RRBR (Romania; 2015), Biorx.si (Slovenia; 2008), BIOBADASER (Spain; 2000), ARTIS (Sweden; 1999), SCQM (Switzerland; 2006), TURKBIO (Turkey; 2011) and 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 harmonised 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 or older, initiation of TNFi as first biological treatment in the period January 1, 2009 to December 31, 2018 and at least one visit (baseline, 6, 12 or 24 months) with any registered PRO while being treated with TNFi. Patients who switched from a 1st to a 2nd TNFi and from a 2nd to a 3rd TNFi, without non-TNFi biological or targeted synthetic DMARD treatment in between, were also included in analyses of

2nd and 3rd TNFi, respectively. Patients with available information on classification criteria were classified as 1) fulfilling the modified New York (NY) criteria for ankylosing spondylitis (AS cohort), or 2) fulfilling the Assessment of SpondyloArthritis International Society (ASAS) criteria but NOT the NY 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 (latest start of first TNFi treatment: December 31st, 2018). Start of follow-up was defined as the date of 1st, 2nd or 3rd TNFi treatment start and end of follow-up was defined as end of 1st, 2nd or 3rd TNFi treatment, end of registry capture or death, whichever came first.

Data collected

Variables collected at start of each TNFi treatment were: age, years since diagnosis, sex, classification criteria (NY and ASAS), body mass index (BMI, kg/m^2), current smoking status, human leucocyte antigen B27 (HLA-B27) status, name of TNFi treatment, physician global, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR, mm/h), Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Metrology Index (BASMI) (25). The following patient-reported outcomes (PROs) were collected at 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 (Patient global), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and the Health Assessment Questionnaire disability index (HAQ)(26–30). The PROs (including BASDAI and BASFI) were registered on a 0-100 mm visual analogue 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 0-10 numeric rating scale (NRS) for pain, fatigue, patient global and physician global; these scores were multiplied by 10 to allow comparison with VAS scores. The 6, 12 and 24 months visits were defined as available visits in the

periods 90 to 270 days, 271 to 545 days and 546 to 910 days, respectively, after start of 1st, 2nd or 3rd 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 or more patients in the cohort had available data.

PRO "remission"

There is no international consensus on cut-off values for PRO remission in axSpA patients. However, in a previous study partial PRO "remission" was defined as pain <20 mm, patient global <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, patient global, BASDAI and BASFI and as HAQ scores ≤0.5. (4,31) Both crude and LUNDEX-adjusted(32) PRO "remission" rates were calculated. The LUNDEX adjustment multiply 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 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, patient global, BASDAI, BASFI and HAQ scores at 6, 12 and 24 months. Secondary outcomes included assessment of the fraction of axSpA patients in PRO "remission" (as defined above) after

6, 12 and 24 months, changes in PRO 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 interquartile ranges) 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.

RESULTS

Patients

We included data on 19,498 biologic-naïve axSpA patients, who constituted the pooled cohort (***All***) for the main analyses. Among these, 3,281 patients were registered to fulfil the modified NY criteria (***AS cohort***) and 993 the ASAS criteria for axSpA and to not fulfill the New York criteria (***nr-axSpA*** cohort) (online supplementary figure S1). Classification criteria were available in 10 of the 15 registries (online supplementary table S1).

In the pooled cohort, adalimumab was the most frequently prescribed 1st TNFi (32%) followed by etanercept (24%), infliximab (22%), golimumab (16%) and certolizumab (6%). Large differences in choice of 1st TNFi were observed across registries (online supplementary table S2). Choice of TNFi were comparable for the 2nd and 3rd TNFi (adalimumab 29%/26%, etanercept 32%/23%, infliximab 13%/16%, golimumab 17%/21% and certolizumab 9%/13%) in the pooled cohorts and in the two sub-cohorts (Table 1).

Baseline characteristics and PROs

Table 1 shows that at baseline the pooled cohort had considerable disease activity as assessed by composite scores and PROs.

Patients starting a 1st TNFi in each of the 15 registries differed considerably with regards to both demographic characteristics, disease activity levels and baseline PROs (online supplementary table S1). The median age at 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 1st TNFi varied between registries (registries with lowest/highest median scores: pain: NOR-DMARD/RRBR: 49/90 mm; fatigue: NOR-DMARD/RRBR and BSRBR-AS: 50/80 mm; patient global: ROB-FIN/RRBR: 50/80 mm; BASDAI: ROB-FIN/RRBR: 42/74 mm; BASFI: ROB-FIN/BSRBR-AS: 28/66 mm, HAQ: NOR-DMARD/RRBR: 0.5/1.9).

Figure 1 demonstrates that the baseline PROs were comparable in the pooled cohort (All) at initiation of the 1st, 2nd and 3rd 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 start of 1st TNFi treatment; pain: 70/70, fatigue: 70/71, patient global: 70/71, BASDAI: 63/64, BASFI: 55/49 and HAQ: 0.9/0.9 (Table 1). Values for physician global, blood tests and composite indexes were also comparable across the two sub-cohorts (Table 1).

PROs after 6, 12 and 24 months of treatment

Figure 2 (upper panel) shows that after 6 months of a 1st 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, patient global, BASDAI, BASFI and HAQ (online supplementary figure S2 a-e). 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/patient global/BASDAI/BASFI/HAQ scores at baseline reported very low scores after 6 months of treatment (online supplementary figure S2 a-e).

In all registries PROs decreased during TNFi treatment (Figure S3), while the absolute values varied considerably. As an example, the highest median pain score after 6 months of 1st TNFi was found in GISEA (40 mm) and lowest in ICEBIO (14 mm).

Large differences in PROs at 6, 12 and 24 months in patients from the pooled cohort treated with the 1st, 2nd and 3rd TNFi, respectively, were observed (Figures 3 and 4 and online supplementary tables S2a-c) with achievement of lower PROs at 6, 12 and 24 months of treatment and larger changes from baseline during the 1st treatment compared to 2nd and 3rd. 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 1st TNFi, 78%/66%/56% for 2nd TNFi and 76%/63%/50% for 3rd TNFi).

The same trend across treatment series was also found in the AS and nr-axSpA cohorts (Figure 4, online supplementary tables S2a-c). 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% Confidence interval (CI) 80-83%) (1st TNFi), while the corresponding rate in nr-axSpA cohort was 69 (67-72)%.

Sensitivity analyses applying LOCF to missing continuous PROs only affected the measures at 12 and 24 months marginally for both 1st, 2nd and 3rd TNFi (online supplementary table S4).

PRO "remission" 6, 12 and 24 months after start of 1st TNFi treatment

After 6 months of 1st 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 and online supplementary table S2a).

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

Similarly, the LUNDEX-adjusted PRO "remission" rates were higher after 6 months of the 1st TNFi treatment compared to the 2nd and 3rd TNFi (online supplementary figure S4, online supplementary table S2a-c).

The AS cohort achieved higher LUNDEX-adjusted "remission" rates for all PROs than the nr-axSpA cohort (Figure 5 and online supplementary table S2a-c).

Concordance of "remission" across PROs in individual patients

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

In online supplementary table S3 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, while "remission" in the functional measures HAQ and BASFI are less concordant with other PROs.

DISCUSSION

In the present study of axSpA patients from 15 European countries, we report for the first time PRO "remission" rates in a large real-world cohort. The disease burden at baseline as assessed by six 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 start of a 1st TNFi the disease burden as experienced by the patients had been markedly reduced (approximately 60%), and a third of patients were in a state of PRO "remission" regarding at least one PRO, i.e., a score ≤20mm. Despite an increasing focus on PROs for the monitoring of axSpA patients, PRO "remission" rates have not previously been reported 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, patient global and BASFI and used similar values for PROs with no recommendations reported in the literature (BASDAI, fatigue). As several registries assess PRO on a 0-10 NRS, we chose to apply a cut-off for "remission" of ≤20. An important 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 that 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 of either AS or 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 patients 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 sub-cohorts of patients with AS according to the NY criteria and patients with nr-axSpA. A challenge with the sub-cohorts is that the classification of patients was performed at enrollment in the registries, typically at the start of 1st TNFi. Thus, a subset of patients in the nr-axSpA cohort may have progressed to AS when they received the 2nd and 3rd 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, i.e., some patients may be 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 in the nr-axSpA cohort, 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 four randomized controlled trials

including 1263 AS patients, which showed that men had a better response to etanercept than women.(47)

A major strength of the present study is the inclusion of >19,000 axSpA patients 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 time points 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 sub-cohorts though the number of patients that could be included in the analyses differed across PRO and follow-up visit. The information captured by the PROs gives a unique understanding of the patients' perspective, which may improve treatment of axSpA patients 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 impact the observed outcomes.

Unfortunately, information on country specific guidelines and recommendations for TNFi treatment of axSpA patients 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, between registry differences in PROs 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 impact 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 due to 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 1st TNF 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 towards 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 axial spondyloarthritis showed heterogeneity in baseline characteristics and PROs between registries, and clear effects of TNFi treatment across registries, diagnostic sub-cohorts and treatment series. The highest PRO remission rates were seen in those fulfilling the modified New York criteria and patients treated with their 1st TNFi.

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FIGURE LEGENDS

Figure 1. Median patient-reported outcome scores for the pooled cohort and in the two sub-cohorts for 1st, 2nd and 3rd TNFi treatment at 6, 12 and 24 months after initiation of 1st TNFi treatment.

AS: modified New York criteria for classification of ankylosing spondylitis; nr-axSpA: non-radiographic axial spondyloarthritis; Patient global: Patient's global assessment of disease activity, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, HAQ: Health Assessment Questionnaire.
*HAQ was scored on a scale ranging from 0-3 and converted to 0-100 for the bar-chart.

Figure 2. Pain, 1st TNFi treatment

Upper figure: Three-dimensional 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 1st TNFi treatment, respectively (z-axis). Lower figures: Stacked bar chart showing the distribution of axSpA patients' pain scores after 6 months of treatment dependent on how the same patients scored at start of TNFi treatment (baseline). Table: No. of patients (%) as illustrated in stacked bar chart.

Figure 3. Radar charts showing axSpA patients' median patient-reported outcome scores at start of TNFi treatment (baseline) and at 6, 12 and 24 months after initiation of treatment with 1st TNFi (baseline, n=19,498), 2nd TNFi (baseline, n=6,304) and 3rd TNFi (baseline, n=1,927).

Patient global: Patient's global assessment of disease activity, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, HAQ: Health Assessment Questionnaire disability index.
*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 (mHAQ) was used.

Figure 4. Changes in patient-reported outcomes from baseline to 6, 12 and 24 months after start of 1st, 2nd and 3rd TNFi treatment in the AS cohort and the nr-axSpA cohort (data as observed).

AS cohort: Patients registered to fulfill the modified New York Criteria for ankylosing spondyloarthritis (AS).
nr-axSpA cohort: Patients registered to fulfill the ASAS criteria for axSpA and to NOT fulfill the modified New York criteria for AS.
Patient global: Patient's global assessment of disease activity, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, HAQ: Health Assessment Questionnaire disability index.
*HAQ was scored on a scale ranging from 0-3; In NOR-DMARD a modified version of HAQ (mHAQ) was used.

Figure 5. PRO "remission" rates (%), 6, 12 and 24 months after start of 1st TNFi treatment for the full cohort and the two sub cohorts.

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)
NY: modified New York criteria for classification of ankylosing spondylitis; nr-axSpA: non-radiographic axial spondyloarthritis; Patient global: Patient's global assessment of disease activity, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, HAQ: Health Assessment Questionnaire disability index. In NOR-DMARD a modified version of HAQ (mHAQ) was used.

Online supplementary figure S1. VENN diagram showing the number of patients in the full axial spondyloarthritis (axSpA) cohort, number of patients that fulfill the Assessment of SpondyloArthritis International Society (ASAS) criteria for axSpA and the number of patients in the AS cohort and the nr-axSpA cohort.

As some registries only assess ASAS – but not the modified New York criteria, a subset of the ASAS cohort could not be classified as having AS or nr-axSpA.
AS cohort: Patients who fulfill the modified New York criteria for ankylosing spondylitis (AS); nr-axSpA cohort: patients who fulfill the ASAS criteria for axSpA and NOT the modified New York criteria for AS.
ASAS cohort: patients who fulfill the ASAS criteria.

Online supplementary figure S2 a. Fatigue, 1st TNFi treatment

Upper figure: Three-dimensional bar chart of the relative frequency (y-axis) of fatigue scores (mm given on x-axis) at baseline and after 6, 12 and 24 months of 1st TNFi treatment, , respectively (z-axis). Lower figure: Stacked bar chart showing the distribution of axSpA patients' fatigue scores after 6 months of treatment dependent on how the same patients scored at start of TNFi treatment (baseline). Table: Percentages as illustrated in stacked bar chart.

Online supplementary figure S2 b. Patient global, 1st TNFI treatment

Upper figure: Three-dimensional bar chart of the relative frequency (y-axis) of patient global scores (mm given on x-axis) at baseline and after 6, 12 and 24 months of 1st TNFi treatment, respectively (z-axis). Lower figure: Stacked bar chart showing the distribution of axSpA patients' patient global scores after 6 months of treatment dependent on how the same patients scored at start of TNFi treatment (baseline). Table: Percentages as illustrated in stacked bar chart.

Online supplementary figure S2 c. BASDAI, 1st TNFi treatment

Upper figure: Three-dimensional bar chart of the relative frequency (y-axis) of BASDAI scores (mm given on x-axis) at baseline and after 6, 12 and 24 months of 1st TNFi treatment, respectively (z-axis). Lower figure: Stacked bar chart showing the distribution of axSpA patients' BASDAI scores after 6 months of treatment dependent on how the same patients scored at start of TNFi treatment (baseline). Table: Percentages as illustrated in stacked bar chart.

Online supplementary figure S2 d. BASFI, 1st TNFi treatment

Upper figure: Three-dimensional bar chart of the relative frequency (y-axis) of BASFI scores (mm given on x-axis) at baseline and after 6, 12 and 24 months of 1st TNFi treatment, respectively (z-axis). Lower figure: Stacked bar chart showing the distribution of axSpA patients' BASFI scores after 6 months of treatment dependent on how the same patients scored at start of TNFi treatment (baseline). Table: No. of patients (%) as illustrated in stacked bar chart.

Online supplementary figure S2 e. HAQ, 1st TNFi treatment

Upper figure: Three-dimensional bar chart of the relative frequency (y-axis) of HAQ scores (units given on x-axis) at baseline and after 6, 12 and 24 months of 1st TNFi treatment, respectively (z-axis). Lower figure: Stacked bar chart showing the distribution of axSpA patients' HAQ scores after 6 months of treatment dependent on how the same patients scored at start of TNFi treatment (baseline). Table: Percentages as illustrated in stacked bar chart.

Online supplementary figure S3. Pain, fatigue, patient global, BASDAI, BASFI and HAQ by registry for axial spondyloarthritis patients at 0, 6, 12 and 24 months after start of 1st TNFi treatment.

The median PRO scores were only presented for timepoints with PROs reported by ≥50 patients.
Patient global: Patient's global assessment of disease activity, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, HAQ: Health Assessment Questionnaire disability index.
Pain, fatigue, patient global, BASDAI, BASFI and physician global were scored on a 0-100 mm visual analogue scale (VAS). Three registries (RRBR, biorx.si and SCQM) used a 0-10 numeric rating scale (NRS) for pain, fatigue, patient global and physician global. For ARTIS, only 6, 12, and 12 month data were available. *HAQ was scored on a scale ranging from 0-3; in NOR-DMARD a modified version of HAQ (mHAQ) was used.

Online supplementary figure S4. PRO "remission" rates (%), 6, 12 and 24 months after 2nd and 3rd TNFi treatment start for the full cohort (all) and the two sub-cohorts.

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)
NY: modified New York criteria for classification of ankylosing spondylitis; nr-axSpA: non-radiographic axial spondyloarthritis; Patient global: Patient's global assessment of disease activity, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, HAQ: Health Assessment Questionnaire disability questionnaire.

Table 1. Baseline characteristics of 19,498 axial spondyloarthritis patients at start of 1st TNFi treatment.

	Started 1st TNFi treatment January 1, 2009 to December 31, 2018[a]					
	All (n=19,498)		AS cohort (n=3,281)[b]		nr-axSpA cohort (n=993)[c]	
Characteristic	**No. of patients with available data**	**Median (IQR) or n (%)**	**No. of patients with available data**	**Median (IQR) or n (%)**	**No. of patients with available data**	**Median (IQR) or n (%)**
Age at TNFi start, years	19498 (100%)	41 (33-51)	3281 (100%)	44 (35-54)	993 (100%)	40 (32-49)
Age at diagnosis, years	16251 (83%)	35 (27-44)	3200 (98%)	35 (28-45)	981 (99%)	36 (28-45)
Years since diagnosis	16251 (83%)	2 (0-8)	3200 (98%)	4 (1-11)	981 (99%)	1 (0-4)
Men	19498 (100%)	11401 (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	16801 (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%)
1st TNFi drug (EMA approval)	19498 (100%)		3281		993	
- Infliximab (1999)		4307 (22%)		542 (17%)		133 (13%)
- Etanercept (2000)		4659 (24%)		738 (22%)		184 (18%)
- Adalimumab (2003)		6278 (32%)		1313 (40%)		392 (39%)
- Certolizumab (2009)		1167 (6%)		108 (3%)		42 (4%)
- Golimumab (2009)		3087 (16%)		580 (18%)		242 (24%)
1st TNFi start, year	19498 (100%)		3281		993	
- 2009-2014		10430 (53%)		1711 (52%)		581 (58%)
- 2015-2018		9068 (47%)		1570 (48%)		412 (42%)
Patient-reported outcomes[d]						
Pain, mm	12641 (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)
Patient global, mm	13059 (67%)	66 (48-80)	1842 (56%)	70 (50-81)	716 (72%)	71 (57-83)
BASDAI, mm	12641 (63%)	58 (42-72)	2066 (63%)	63 (49-76)	655 (66%)	64 (49-76)
BASFI, mm	10095 (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						
- Physician global, mm	7988 (41%)	41 (23-60)	1046 (32%)	50 (30-68)	478 (48%)	45 (30-60)

Blood tests						
- CRP, mg/l	13154 (67%)	8 (3-20)	2112 (64%)	10 (3-23)	698 (70%)	6 (2-17)
- ESR, mm/hr	10547 (54%)	18 (8-33)	1592 (49%)	23 (10-40)	329 (33%)	13 (6-31)
Composite indices						
- 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)

NY: modified New York criteria for classification of ankylosing spondylitis; nr-axSpA: non-radiographic axial spondyloarthritis; IQR: Interquartile Range; BMI: Body Mass Index; HLA-B27: Human Leukocyte Antigen subtypes B*2701-2759; EMA: European Medicines Agency; TNFi: Tumor Necrosis Factor-alpha inhibitor; Patient global: Patient's global assessment of disease activity; HAQ: Health Assessment Questionnaire disability index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; Physician global: Physician Global assessment; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASMI: Bath Ankylosing Spondylitis Metrology Index.

[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 modified New York Criteria for ankylosing spondyloarthritis (AS), initiating treatment after 2009.

[c]Patients registered to fulfill the Assessment of SpondyloArthritis International Society (ASAS) criteria for axSpA and to NOT fulfill the modified New York criteria for AS (nr-axSpA), initiating treatment after 2009.

[d]Pain, fatigue, patient global, BASDAI, BASFI and physician global were scored on a 0-100 mm visual analogue scale (VAS); HAQ was scored on a scale ranging from 0-3. Three registries (RRBR, biorx.si and SCQM) used a 0-10 numeric rating scale (NRS) for pain, fatigue, patient global and physician global.

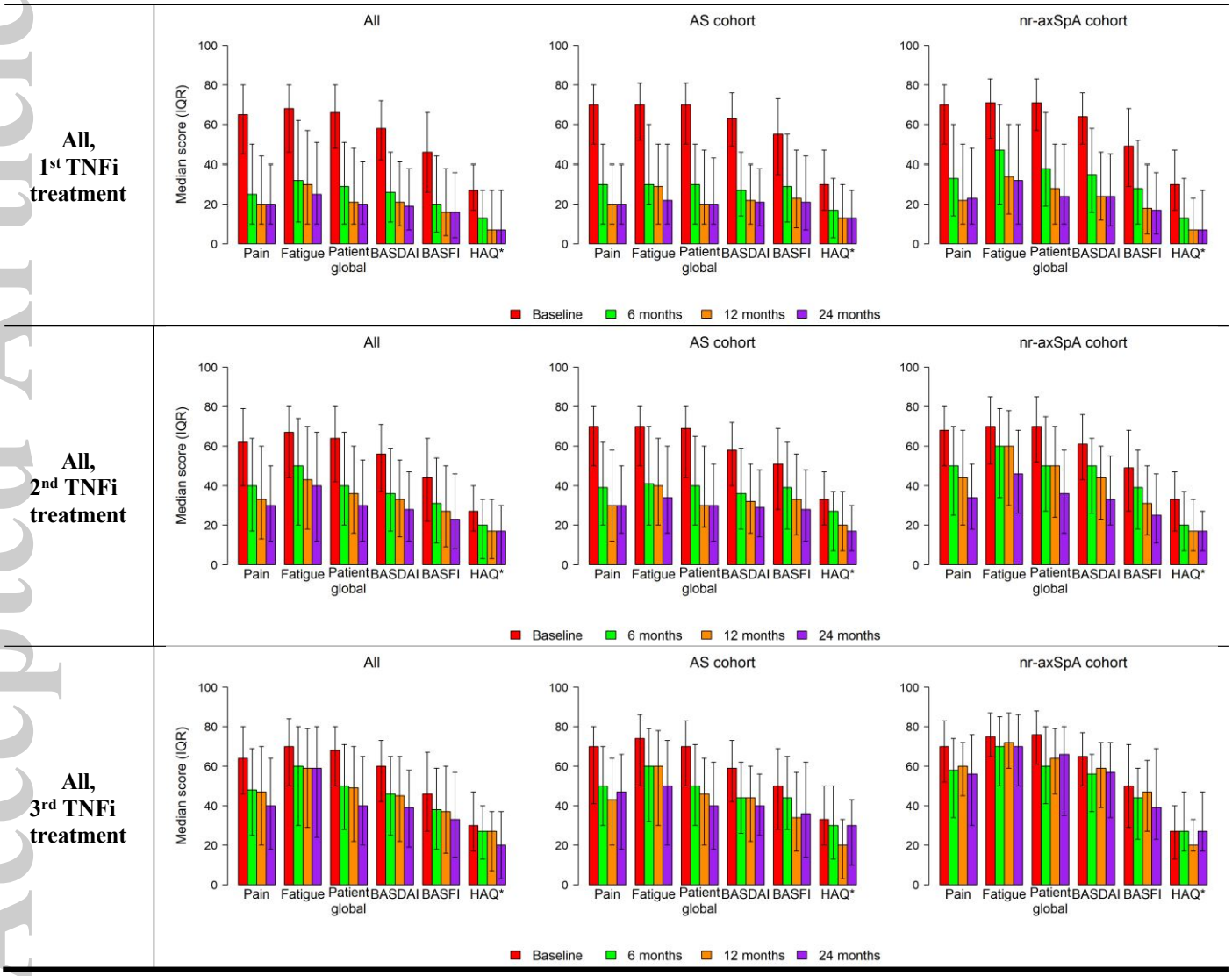
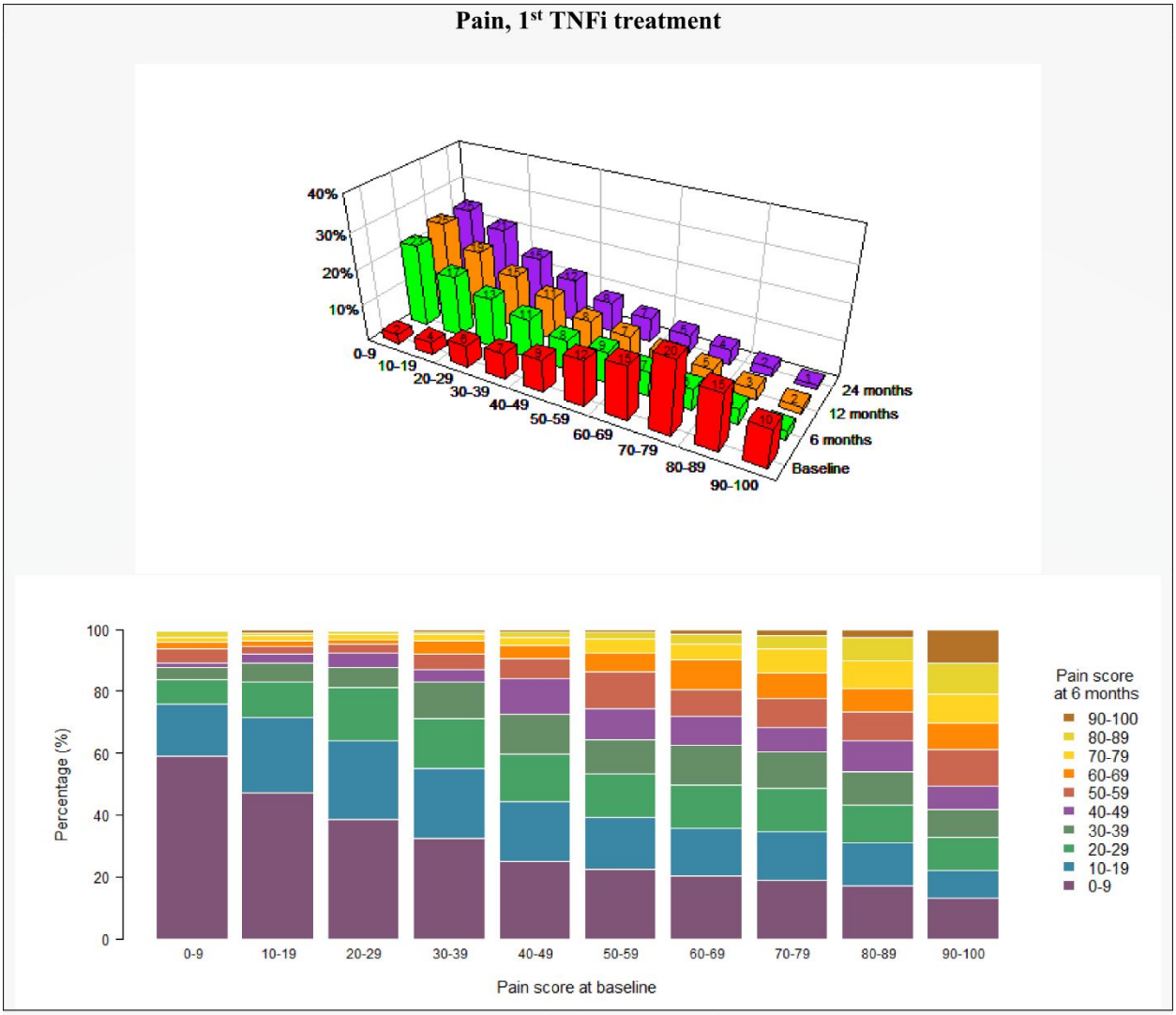


Figure 1. Median patient-reported outcome scores for the pooled cohort and in the two sub-cohorts for 1st, 2nd and 3rd TNFi treatment at 6, 12 and 24 months after initiation of 1st TNFi treatment.

AS: modified New York criteria for classification of ankylosing spondylitis; nr-axSpA: non-radiographic axial spondyloarthritis; Patient global: Patient's global assessment of disease activity, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, HAQ: Health Assessment Questionnaire.

*HAQ was scored on a scale ranging from 0-3 and converted to 0-100 for the bar-chart.



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, 1st TNFi treatment. Upper figure: Three-dimensional bar chart of the relative frequency (y-axis) of pain (mm given on x-axis) among all axSpA patients at baseline and 6, 12 and 24 months after start of 1st TNFi treatment (z-axis). Lower figures: Stacked bar chart showing the distribution of axSpA patients' pain scores after 6 months of treatment dependent on how the same patients scored at start of TNFi treatment (baseline).

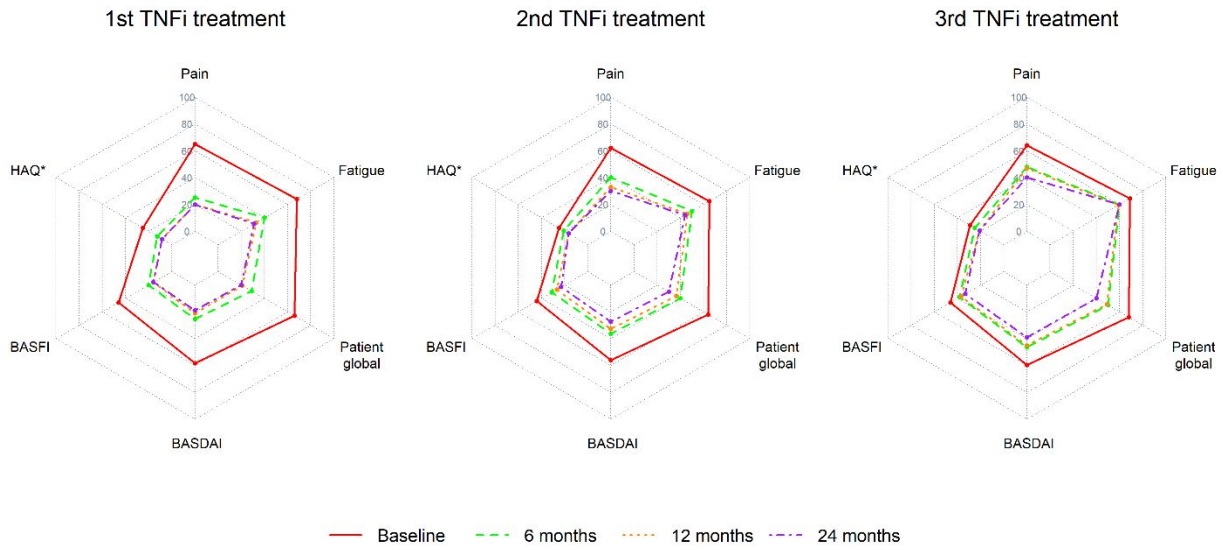


Figure 3. Radar charts showing axSpA patients' median patient-reported outcome scores at start of TNFi treatment (baseline) and at 6, 12 and 24 months after initiation of treatment with 1st TNFi (baseline, n=19,498), 2nd TNFi (baseline, n=6,304) and 3rd TNFi (baseline, n=1,927).

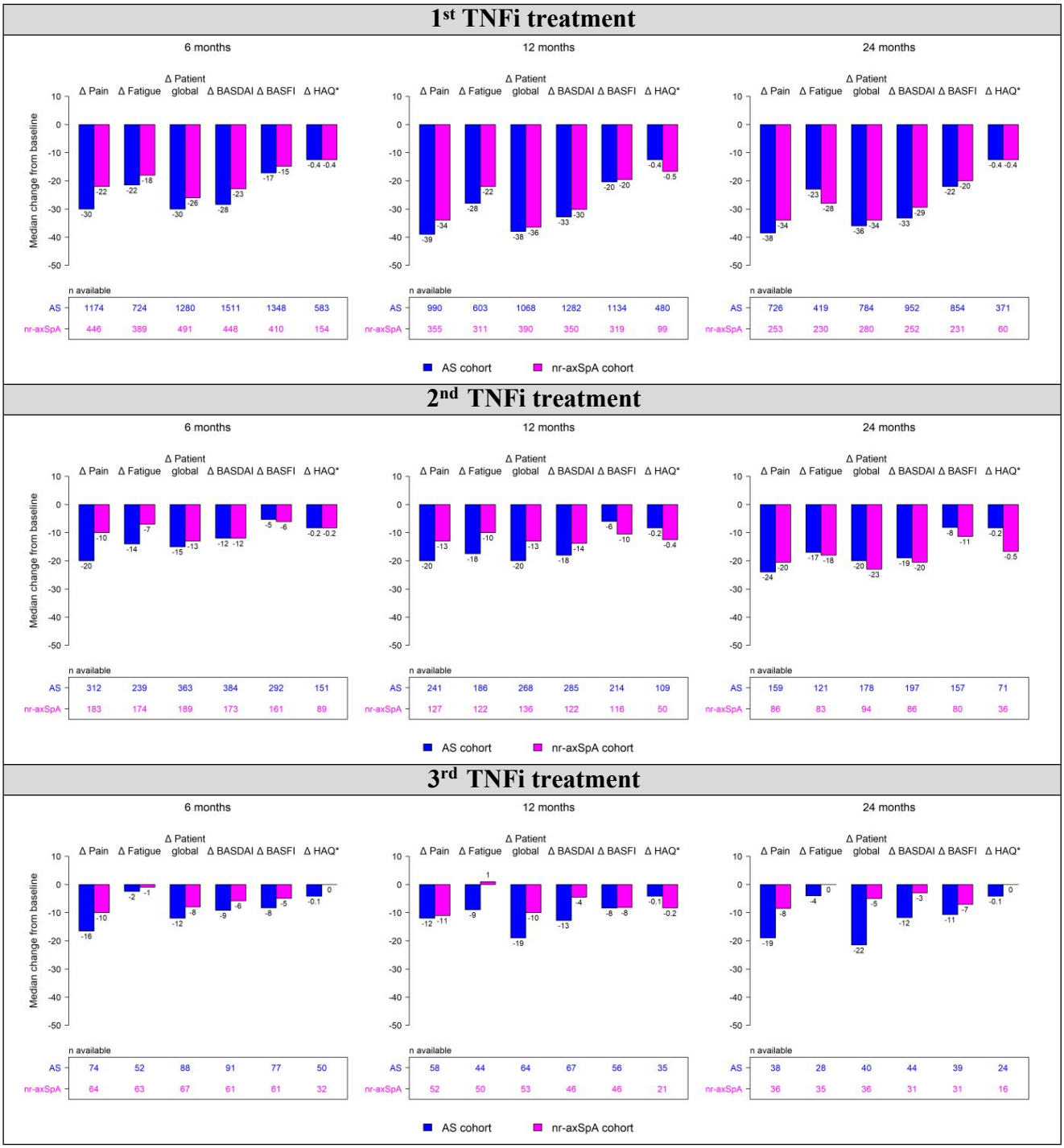


Figure 4. Changes in patient-reported outcomes from baseline to 6, 12 and 24 months after start of 1st, 2nd and 3rd TNFi treatment in the AS cohort and the nr-axSpA cohort (data as observed).