Quality of life and therapeutic management of axial spondyloarthritis patients in Italy: a 12-month prospective observational study

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Abstract

Objective

To evaluate the health-related quality of life (HRQoL), disease activity, treatment adherence, and work ability in the real-world setting in patients with axial spondyloarthritis (axSpA).

Methods

QUASAR was a prospective 12-month, observational study involving 23 rheumatology centres across Italy, including adult patients with axSpA according to the Assessment of SpondyloArthritis International Society (ASAS) criteria. Patients were followed at baseline, 3, 6, and 12 months for disease activity and health-related QoL (HRQoL), treatment adherence and work ability. Regression analysis was used to assess the association between treatment and outcome variables.

Results

413 (80.7%) out of axSpA 512 patients were diagnosed with ankylosing spondylitis (AS) and 99 (19.3%) with non-radiographic axSpA (nr-axSpA). Nr-axSpA and AS patients had similar baseline disease activity and HRQoL. Biologic disease-modifying anti-rheumatic drugs (bDMARDs) were the most frequent medication (n=426, 83.2%). Over the 1-year follow-up, disease activity measures (joint pain and swelling, CRP, global assessment, BASDAI, ASDAS), HRQoL and work ability significantly improved, while few differences emerged between nr-axSpA and AS patients. Treatment satisfaction and adherence questionnaires improved over the 12 months. Patients treated with bDMARDs showed improved outcomes for disease activity measures and HRQoL variables, greater benefit observed in patients with AS.

Conclusion

We found clinical and HRQoL improvement over 1 year in a large, real-world population of nr-axSpA and AS patients treated with bDMARDs or conventional synthetic DMARDs.

Key words

ankylosing spondylitis, non-radiographic axial spondyloarthritis, health-related quality of life, epidemiology, Italy

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Competing interests: see page 969.

Introduction

Axial spondyloarthritis (axSpA) is a debilitating chronic inflammatory disease characterised by inflammation and bone formation in the sacroiliac joints and spine (1-3).

Patients with axSpA include those with radiographic axSpA (ankylosing spondylitis; AS), defined on simple pelvic radiograph, according to the modified New York criteria, and those who do not present changes in radiograph (non-radiographic axial spondyloarthritis; nr-axSpA) (1, 4).

The relationship between nr-axSpA and AS is still heavily debated (5-7). About 10-20% of patients diagnosed with nr-axSpA go on to develop AS within 2 years, whereas about 30% may never develop radiographic changes typical of AS over time (8, 9).

Treatment options for axSpA include non-steroidal anti-inflammatory drugs (NSAIDs) and biologic disease-modifying anti-rheumatic drugs (bDMARDs) that target tumour necrosis factor (TNF) (10) or interleukin (IL)-23/17 axis (11, 12). However, to date, only anti-TNFs have been licensed in patients with nr-axSpA (13).

In real-world clinical practice, TNF inhibitors are used to a lesser extent in patients with nr-axSpA compared to those with AS (6, 7). Differences between nr-axSpA and AS with regard to the effect of treatment, clinical measures, humanistic, and economic burden have recently been examined in a systematic review (5). Despite confirming already established differences such as higher levels of C-reactive protein (CRP) in AS patients (14) and the lower extent of structural damage and slower radiographic progression in nr-axSpA, patient-reported outcome measures, including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (15), Ankylosing Spondylitis Disease Activity Score (ASDAS) (16), and health-related quality of life (HRQoL) were similar in those with AS and nr-axSpA, suggesting similar clinical and QoL burden.

Randomised controlled trials are of limited use in quantifying disease burden, as they have minimal external validity, protocol-related costs associated with unrealistic treatment patterns and a non-representative patient population. Consequently, real-world evidence is an integral source of data relating to burden of disease. To address this, the Italian observational QUality of life in patients with Axial SpondyloARthritis (QUASAR) study was undertaken. This multicentre observational study assesses the evolution of disease activity and HRQoL in patients suffering from the 2 forms of axSpA over a 12-month period and whether treatment can improve these outcomes.

Patients and methods

Patient population

Patients were included in the QUASAR study (17) if a) aged ≥18 years and classified with axSpA according to the Assessment of SpondyloArthritis International Society (ASAS) axSpA criteria (1) and b) capable of understanding and completing the questionnaires. Exclusion criteria included participation in a clinical study for the treatment of axSpA or a life expectancy of ≤1 year. This study was approved by each institutional ethics committee and all patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki. Clinical sites were selected on the basis of the availability of an adequate number of subjects affected by axSpA, implementation of the ASAS 2009 criteria (1) in routine clinical practice and the availability of an internet connection.

Disease activity measures

Assessment measures used to collect data in the QUASAR study have previously been described in detail (17). In brief, data were collected at the study entry (baseline) and after 3, 6, and 12 months. At each outpatient visit, disease activity was assessed using the ASDAS, BASDAI, Patient's Global Assessment of Disease Activity (PtGA) on a 0 to 10 cm visual analogue scale (VAS), the Physician's Global Assessment of Disease Activity (PhGA) on a 0 to 10 cm VAS. The presence of dactylitis, enthesitis and axSpA symptoms (inflammatory spinal pain and stiffness) were also assessed.

With regard to concomitant medication

from different categories, a hierarchy of importance was used for the evaluation of the effect of treatment on disease activity and QoL. The following was adopted in the analysis: bDMARDs > csDMARDs > NSAIDs. Therefore, a patient receiving a bDMARD plus a csDMARD was included in the bDMARD group. In contrast, for the assessment of treatment satisfaction and adherence, each patient was assigned to a specific drug category based on which medication he/she deemed was more relevant.

Treatment satisfaction and adherence

Treatment satisfaction and treatment adherence were assessed using the treatment satisfaction (visual analogue scale, VAS) and 5-item Medication Adherence Rating Scale (MARS-5) questionnaires (18). The MARS-5 questionnaire assessed self-reported medication behaviour using 5 questions rated on a 5-point scale, with a score ranging from 5 to 25 points. A score of 25 is considered adherent and a score of <25 has been considered to indicate non-adherence (18).

HRQoL questionnaires

HRQoL and work productivity were assessed using the Ankylosing Spondylitis Quality of Life (ASQoL) (19) and EuroQoL 5-Dimension 5-Level (EQ-5D-5L) (20). The ASQoL questionnaire measures the impact of axSpA on HRQoL from the patient perspective (19). Total scores range from 0 to 18, higher scores indicating poor HRQoL. The EQ-5D-5L is a generic tool measuring HRQoL and is composed of 2 parts: a descriptive system and a VAS (20]. The descriptive system includes 5 single-item dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) to describe the health status of the subject. The VAS evaluates general health on a continuous response scale ranging from 0 (worst possible health state) to 100 (best possible health state).

Work productivity and activity impairment (WPAI) questionnaire

The Work Productivity and Activity Impairment (WPAI) questionnaire was used to measure the effect of overall health and specific symptoms on productivity at work and outside work (21). The WPAI-GH (General Health) consists of 6 items evaluating 4 domains in the previous 7 days: 1) activity impairment (percentage impairment in daily activities), 2) overall work productivity loss, 3) presenteeism (percentage of impairment experienced at work due to health problems) and 4) absenteeism (percentage of working time missed

Table I. Baseline clinical characteristics of the entire patient population and after subgrouping according to the presence of radiographic changes.

Variable	All patients (n=512)	nr-axSpA patients (n=99)	AS patients (n=413)	*p*-value
Age	47.8 ± 13.1	42.5 ± 13.4	49.0 ± 12.7	**<0.001**
Males, n (%)	318 (62.1)	53 (53.5)	265 (64.2)	0.065
Smokers, n (%)	125 (24.4)	20 (20.2)	105 (25.4)	0.3
Age at diagnosis, years	39.5 ± 13.0	37.8 ± 13.0	39.9 ± 13.0	0.15
Time to diagnosis, years*	5.4 ± 7.2	3.8 ± 5.7	5.8 ± 7.4	**0.004**
Time from onset, years	13.7 ± 10.3	8.4 ± 8.2	14.9 ± 10.3	**<0.001**
Time from diagnosis, years	8.3 ± 7.3	4.7 ± 5.3	9.1 ± 7.5	**<0.001**
SpA familiarity	97 (18.9)	14 (14.1)	83 (20.1)	0.20
Psoriasis familiarity	108 (21.1)	25 (25.3)	83 (20.1)	0.27
HLA-B27+	249 (48.6)	40 (54.8)	209 (62.2)	0.29
CRP, mg/dL	0.8 ± 2.2	0.7 ± 1.3	0.8 ± 2.4	0.38
Axial pain	300 (58.6)	61 (61.6)	239 (57.9)	0.57
Peripheral manifestations				
Enthesitis	72 (14.1)	14 (14.4)	58 (14.0)	1.00
Dactylitis	3 (0.6)	1 (1.0)	2 (0.5)	0.50
Extra-articular manifestations	263 (51.4)	54 (55.7)	209 (50.4)	0.5
Psoriasis	91 (17.8)	24 (24.2)	67 (16.2)	0.08
Uveitis	84 (16.4)	16 (16.2)	68 (16.5)	1.00
Crohn's disease	35 (6.8)	4 (4.0)	31 (7.5)	0.27
Ulcerative colitis	23 (4.5)	5 (5.0)	18 (4.4)	0.78
Comorbidities	213 (41.6)	39 (40.2)	174 (41.9)	0.65
Hypertension	82 (16.0)	8 (8.1)	74 (17.9)	**0.015**
Allergy	31 (6.1)	10 (10.1)	21 (5.1)	0.11
Anxiety/depression	22 (4.3)	4 (4.0)	18 (11.3)	1.00
Questionnaires				
PhGA	2.8 ± 2.7	2.8 ± 2.5	2.7 ± 2.7	0.64
PtGA	3.6 ± 2.7	4.0 ± 2.6	3.6 ± 2.8	0.057
BASDAI	3.2 ± 2.5	3.6 ± 2.5	3.1 ± 2.4	0.096
ASDAS	2.1 ± 1.1	2.2 ± 1.1	2.1 ± 1.1	0.43
ASQoL	5.8 ± 5.5	6.2 ± 5.5	5.7 ± 5.4	0.39
EQ-5D-5L (VAS)	66.3 ± 21.8	63.3 ± 23.5	67.1 ± 21.3	0.19
Treatment satisfaction (VAS)	73.2 ± 30.2	69.4 ± 33.9	74.1 ± 29.2	0.38
MARS-5	23.8 ± 2.3	23.7 ± 2.6	23.8 ± 2.2	0.29
WPAI	34.8 ± 28.6	37.6 ± 29.4	34.2 ± 28.4	0.3
Treatment				
bDMARDs	426 (83.2)	75 (75.8)	351 (85.0)	**0.035**
csDMARDs	117 (22.9)	25 (25.3)	92 (22.3)	0.51
NSAIDs	85 (16.6)	24 (24.2)	61 (14.8)	**0.034**
Glucocorticoids	27 (5.3)	6 (6.0)	21 (5.1)	0.62
Analgesics	18 (3.5)	1 (1.0)	17 (4.1)	0.22
Other	30 (5.9)	4 (4.0)	26 (6.3)	0.48

Data are reported as mean ± standard deviation or frequencies (n [%]). *p*-value refers to the comparison between the non-radiographic and radiographic axSpA subgroups. AS: ankylosing spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life; axSpA: axial spondyloarthritis; bDMARDs: biologic disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; EQ-5D-5L: EuroQoL 5-Dimension 5-Level; HLA-B27: human leukocyte antigen B27; MARS-5: Medication Adherence Rating Scale; nr-axSpA: non-radiographic axial spondyloarthritis; PhGA: physician global assessment; PtGA: patient global assessment; SpA: spondyloarthritis; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment.

*"Time to diagnosis" refers to time taken from first symptoms experienced to actual diagnosis by a rheumatologist, whereas "time from onset" refers to time passed to date since first onset of symptoms of the disease. "Time from diagnosis" refers to time taken to date since diagnosis was performed.

due to health problems). Higher scores indicate greater work productivity loss and activity impairment.

Statistical analysis

The sample size was calculated by assuming a Pearson's correlation coefficient ranging from 0.3 to 0.8 between the total score of the ASQoL questionnaire and the score of Item 6 of the WPAI-GH questionnaire and calculating the relevant confidence interval (CI), assuming an alpha error equal to 0.05. A sample of 500 patients enrolled at the baseline visit would have allowed data to be obtained from 392 assessable patients, with a maximal CI of ~0.17, assuming 20% of enrolled patients would not complete the study and 2% would complete the study but with missing data for the total score of the ASQoL questionnaire and/or for the Item 6 score of the WPAI-GH questionnaire.

Quantitative variables were described using mean, standard deviation (SD) and qualitative variables through absolute and relative frequencies.

Baseline characteristics were compared using the Fisher exact test or Mann-Whitney test. Multilevel mixed models (linear or logistic regression as appropriate, and using patient as clustering variable) were applied to evaluate the QoL and clinical outcomes (BASDAI, ASDAS-CRP, PhGA, PtGA, treatment satisfaction, ASQoL, EQ5D-VAS, MARS-5 and WPAI) with respect to time during the study and subsequently with respect to the following covariates: type of treatment (as drug class: bDMARDs, csDMARDs, NSAIDs, glucocorticoids, or as single biologic therapies adalimumab, etanercept, golimumab, infliximab), type of axSpA (radiographic and non-radiographic). Statistical analyses were performed using Stata software v. 13 (StataCorp, College Station, TX, USA). A p-value of <0.05 was considered statistically significant.

Results

Baseline clinical characteristics

512 patients were enrolled across 23 Italian centres from May 2014 to April 2015. 425 (83%) patients underwent a visit at 3 months, 462 (90.2%) at 6 months, while 466 (91%) patients underwent the final visit at 12 months. The baseline and clinical characteristics have previously been described in detail (17). A summary of baseline demographic and clinical characteristics is presented in Table I. From the entire cohort of 512 patients, 413 (80.7%) were diagnosed with AS while 99 (19.3%) were diagnosed with nr-axSpA. Patients with AS were slightly older (49.0±12.7 *vs.* 42.5±13.4 years; p<0.001) and a higher proportion were males (64.2%). While the age of disease onset was similar for both groups (approximately 34 years), time to diagnosis, time from onset and time from diagnosis were significantly longer for AS patients (Table I). A higher prevalence of hypertension was observed in AS patients (17.9% *vs.* 8.1%, p=0.015). In terms of baseline disease activity, approximately 60% of patients presented with axial pain, 14% had enthesitis and mean BASDAI and ASDAS values were 3.2±2.5 and 2.1±1.1 respectively, indicating mild disease activity. No differences were observed in terms of baseline disease activity, peripheral or extra-articular manifestations and HRQoL measures between nr-axSpA and AS patients. In all patients, bDMARDs were the most frequently prescribed medication (83.2%), over csDMARDs (22.9%) and NSAIDs (16.6%).

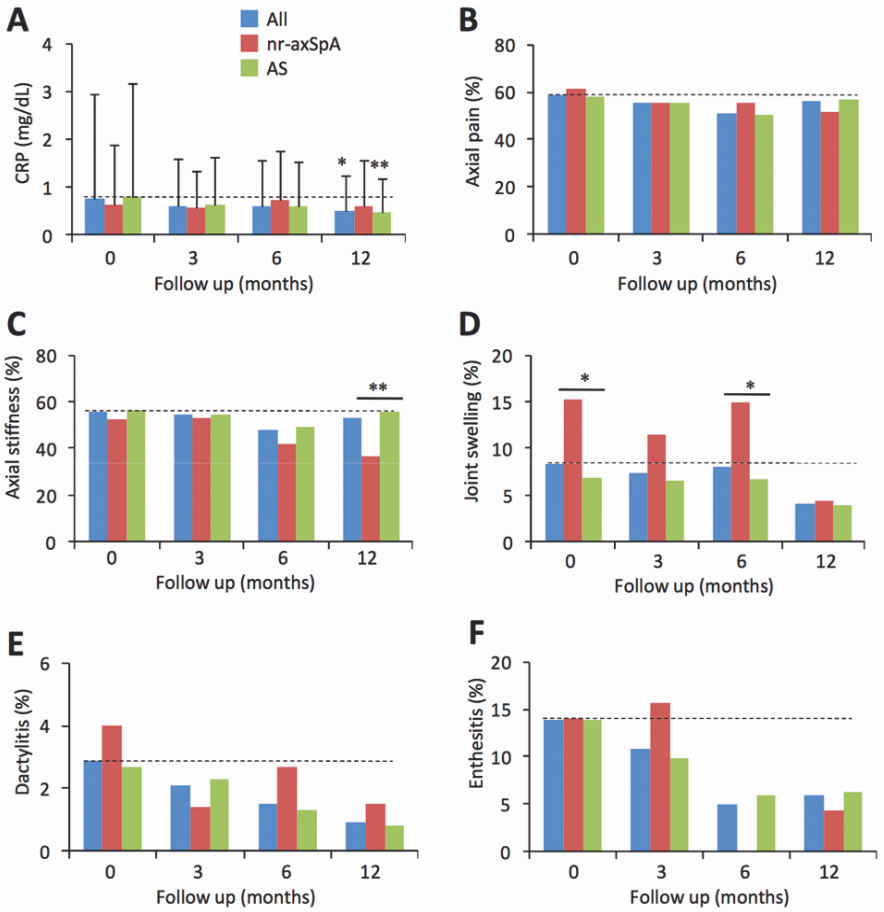

Fig. 1. Disease activity measures and peripheral manifestations in the entire population and by disease subgroups.

Data are presented as mean ± SD for continuous variables (*i.e.* CRP) and % for the frequency of all other disease activity variables.

AS: ankylosing spondylitis; CRP: C-reactive protein; nr-axSpA: non-radiographic axial spondyloarthritis. Asterix denote statistically significant differences compared to baseline (0 months) visit where *<0.05, **<0.01.

Differences between nr-axSpA and AS subgroups are also represented by asterix and horizontal bars. Horizontal hatched line represents whole series levels at baseline to aid visual detection of changes (*vs.* baseline) over subsequent visits.

Treatment over the follow-up period

The rate of medication was unchanged over the follow-up period; the major-

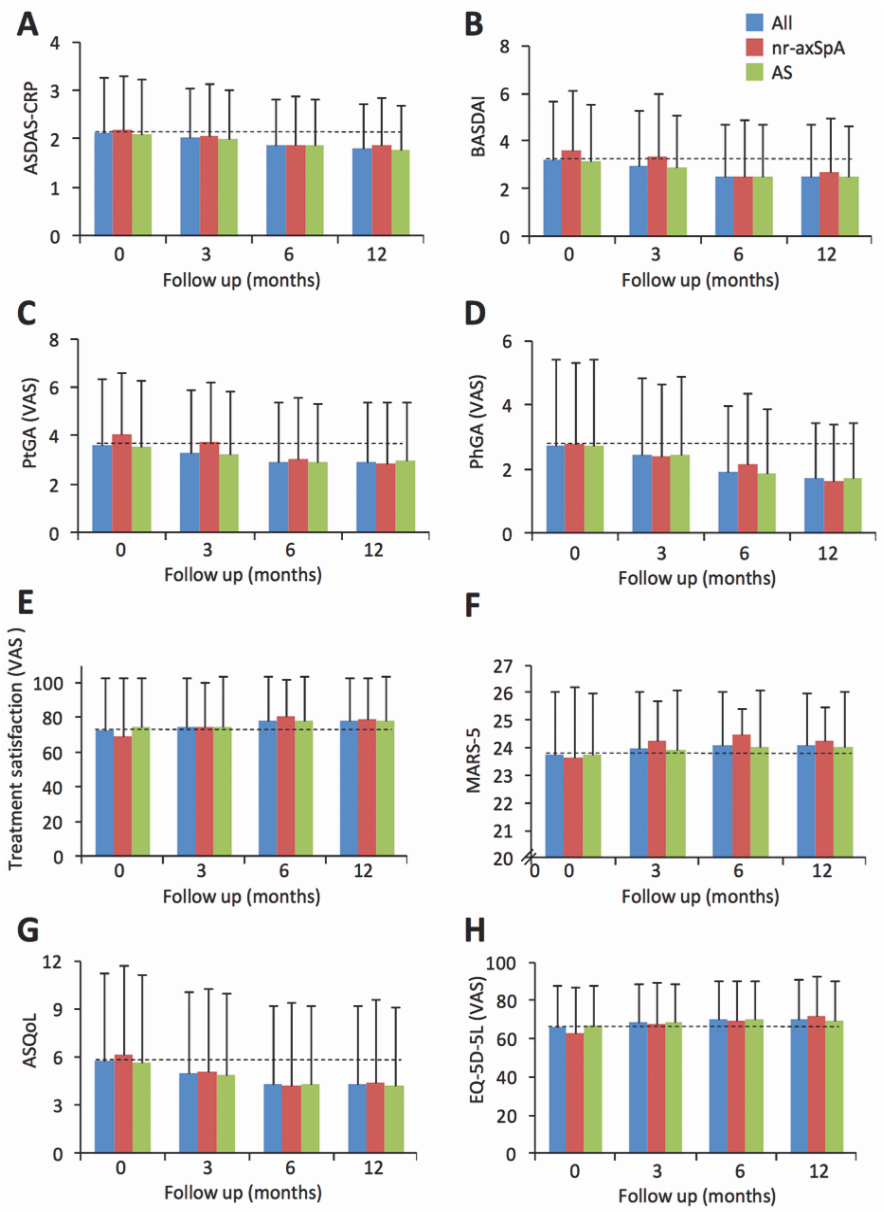

Fig. 2. Disease activity measures based on questionnaires, treatment satisfaction, treatment adherence and QoL in the entire population and by disease subgroups.
Data are presented as mean ± SD.
AS: ankylosing spondylitis; ASQoL: Ankylosing Spondylitis Quality of Life; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; EQ-5D-5L: EuroQoL 5-Dimension 5-Level; MARS-5, Medication Adherence Report Scale-5; nr-axSpA: non-radiographic axial spondyloarthritis. PhGA: physician global assessment; PtGA: patient global assessment; VAS: visual analogue scale.
Horizontal hatched line represents whole series levels at baseline to aid visual detection of changes (*vs*. baseline) over subsequent visits. Asterix denote statistically significant differences compared to baseline (0 months) visit where *<0.05, **<0.01.

ity of patients were treated with bDMARDs (83.2% at baseline *vs*. 85.6% at 12 months) followed by csDMARDs (22.9% at baseline *vs*. 24.7% at 12 months; mainly methotrexate and sulfasalazine) and NSAIDs (16.6% at baseline *vs*. 18% at 12 months). As observed at baseline, a slightly higher proportion of AS patients received bDMARDs compared to nr-axSpA patients, maintaining statistical significance at 12 months (86.9% *vs*. 77.9%, $p<0.001$).

Disease activity over the follow-up period

Changes in disease activity measures and peripheral manifestations over the follow-up period are shown in Figure 1. CRP levels decreased significantly in all patients over the 12 months ($p<0.01$) with significant differences observed between levels at baseline and 12 months for the entire patient population as well as the AS subgroup (0.81±2.4 *vs*. 0.49±0.68 mg/dl, $p<0.01$, Fig. 1A). While a generalised reduction in axial pain was observed among patients over the 12 months, this was not statistically significant (Fig. 1B). Localisation of axial pain was more frequently observed in the lumbar region (65–70% of patients). While axial stiffness decreased over the study period in nr-axSpA patients ($p=0.008$), this was not observed in AS patients (Fig. 1C). A higher number of nr-axSpA patients presented with joint swelling at 0 and 6 months compared to AS patients, decreasing to a similar extent in both groups at 12 months (Fig. 1D). The presence of dactylitis and enthesitis significantly reduced in all patients over the 12 months, from 3% to 1% for dactylitis ($p=0.004$) and from 14% to 6% for enthesitis ($p<0.001$) (Fig. 1E-F).
Results from ASDAS-CRP, BASDAI, PtGA and PhGA questionnaires over the follow-up period are presented in Fig. 2A-D. A statistically significant reduction over the 12 months ($p<0.01$ for all measures) was observed for all 4 disease activity measures, with no significant difference observed between nr-axSpA and AS patient subgroups (Fig. 2A-D).

Treatment satisfaction, adherence and HRQoL

Treatment satisfaction (VAS) and adherence (MARS-5) questionnaires revealed a time-dependent improvement over the 12 months in all patients (VAS: $p<0.01$ both at 6 and 12 months; MARS-5: $p=0.030$ at 3 months and $p<0.01$ both at 6 and 12 months) (Fig. 2E-F). A similar improvement was also observed for ASQoL ($p<0.01$) and EQ-5D-5L questionnaires ($p<0.01$) (Fig. 2G-H). No difference was detected between nr-axSpA and AS patient subgroups for treatment or HRQoL questionnaires over the 12 months.
Treatment adherence was also observed to improve some disease activity measures; both BASDAI (2.2±2.1

Table II. WPAI domains for the entire population and by radiographic involvement.

Treatment	Follow-up period				*p*-value
	Baseline	3 months	6 months	12 months	
Total					
Total activity impairment	34.8 ± 28.6	31.0 ± 27.0	29.4 ± 26.6	29.2 ± 26.0	**<0.001**
Work productivity loss	30.2 ± 27.9	25.5 ± 24.6	27.1 ± 26.1	24.8 ± 24.4	**0.028**
Presenteeism	27.3 ± 27.5	23.5 ± 24.4	24.5 ± 26.14	21.9 ± 23.07	**0.018**
Absenteeism	6.3 ± 15.8	5.4 ± 16.7	8.0 ± 21.3	7.4 ± 18.98	0.36
nr-axSpA					
Total activity impairment	37.6 ± 29.4	32.3 ± 26.5	27.9 ± 25.6	27.1 ± 26.6	**<0.001**
Work productivity loss	36.7 ± 29.7	26.9 ± 27.2	29.5 ± 30.8	25.4 ± 28.9	**0.001**
Presenteeism	32.3 ± 27.8	25.1 ± 25.1	26.1 ± 29.1	20.3 ± 25.3	**0.004**
Absenteeism	8.1 ± 17.2	5.8 ± 19.8	5.8 ± 14.4	8.7 ± 19.4	0.67
Radiographic					
Total activity impairment	34.2 ± 28.4	30.7 ± 27.1	29.7 ± 26.8	29.5 ± 25.9	**<0.001**
Work productivity loss	28.6 ± 27.3	25.2 ± 24.0	26.6 ± 25.0	24.7 ± 23.4	0.37
Presenteeism	26.1 ± 27.4	23.2 ± 24.3	24.2 ± 25.5	22.3 ± 22.7	0.21
Absenteeism	6.0 ± 15.5	5.39 ± 16.0	8.4 ± 22.6	7.27 ± 18.9	0.25

p-value refers to difference over time for each patient population. Statistically significant differences are highlighted in bold.
WPAI: work productivity and activity impairment.

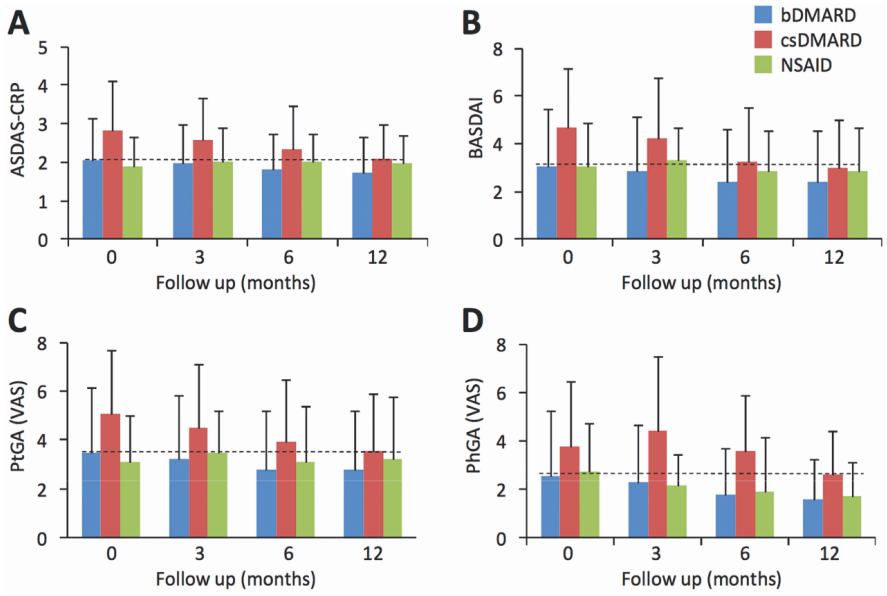

Fig. 3. Effect of bDMARDs, csDMARDs and NSAIDs on disease activity measures.
Data are presented as mean ± SD.
ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; PhGA: physician global assessment; PtGA: patient global assessment; VAS: visual analogue scale. Horizontal hatched line represents bDMARD levels at baseline to aid visual detection of changes (*vs*. baseline) over subsequent visits.

vs. 2.9±2.1, *p*=0.001) and ASDAS-CRP (1.7±0.9 *vs*. 1.9±0.9, *p*=0.005) were significantly improved after 12 months in adherent patients (MARS score = 25) *vs*. non-adherent patients (MARS-5 score <25) compared to baseline levels.

Work productivity and activity impairment

We next evaluated work productivity and activity impairment in nr-axSpA and AS patients over the 12 months. Results for the 4 domains, total activity impairment, work productivity loss, presenteeism and absenteeism are summarised in Table II. For the whole population and for nr-axSpA patients, a statistically significant decrease over the 12 months ($p<0.001$, for both populations) was observed for WPAI (Q6, total activity impairment) as well as presenteeism, whereas a significant decrease was only observed for work productivity loss in AS patients.

Class of medication, disease activity and HRQoL variables

Based on the similar burden of disease activity and HRQoL observed between nr-axSpA and AS patients (Fig. 1 and 2), we decided to consider both subgroups of patients together for all further analysis to evaluate the effect of treatment on specific outcome measures, while also avoiding potential pitfalls attributed to insufficient sample size from excessive sub-analysis. We next evaluated the effect of the most frequently used classes of drugs: bDMARDs, csDMARDs and NSAIDs. Patients treated with bDMARDs remained the same (83.2% at baseline *vs*. 85.6% at 12 months), as well as those treated with csDMARDs were 7.2% at baseline and 6.2% at 12 months, and those treated with NSAIDs were 5.4% and 4.5%, respectively, at baseline and 12 months.

Analysing, over the follow-up period, the disease activity and HRQoL variables by each single treatment, a significant improvement was observed for ASDAS-CRP and BASDAI, both for bDMARDs and csDMARDs, and for PtGA, PhGA, treatment satisfaction-VAS, ASQoL, EQ-5D-5L and WPAI for bDMARDs, whereas this was not observed for other treatments

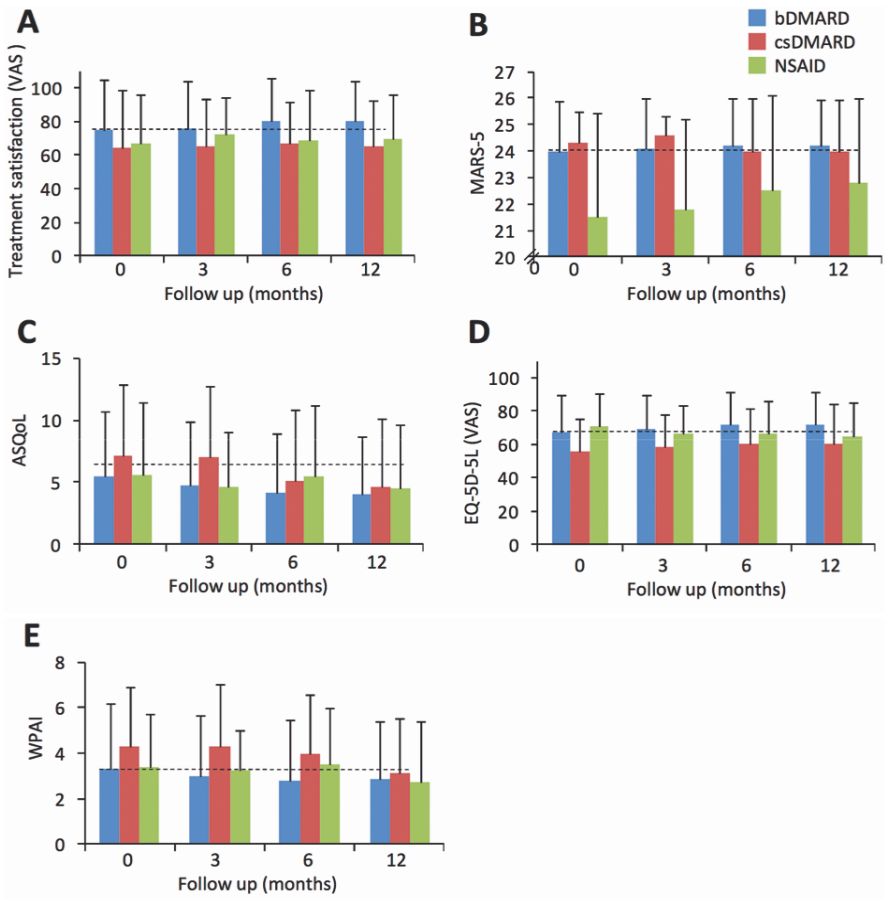

Fig. 4. Effect of bDMARDs, csDMARDs and NSAIDs on treatment satisfaction and work ability measures. Data are presented as mean ± SD.
ASQoL: Ankylosing Spondylitis Quality of Life; EQ-5D-5L: EuroQoL 5-Dimension 5-Level; MARS-5: Medication Adherence Report Scale-5; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment.
Horizontal hatched line represents bDMARD levels at baseline to aid visual detection of changes (*vs.* baseline) over subsequent visits.

(Fig. 3 and 4). Patients treated with csDMARDs tended to present with a higher burden of disease (Fig. 3A-B; ASDAS-CRP and BASDAI) and lower treatment satisfaction compared to bDMARDs and NSAIDs (Fig. 4A) although in the latter it was not statistically significant. Patients treated with bDMARDs significantly improved disease activity and HRQoL measures compared to those receiving csDMARDs or NSAIDs.

A multivariate mixed linear regression model was next performed (considering time of follow-up visits and classes of treatments as covariates) revealing that bDMARDs *versus* csDMARDs were significantly associated with an improvement in ASDAS-CRP, BASDAI, PtGA, PhGA, treatment satisfaction (VAS), EQ-5D-5L (all with $p<0.001$) and WPAI ($p=0.012$), independently of time in the study (Supplementary file, Table S1).

Effect of duration of bDMARD treatment on disease activity and HRQoL variables

Based on the observation that patients treated with bDMARDs benefitted to a greater extent over csDMARDs or NSAIDs (Fig. 3, 4, and Suppl. Table S1), we next wanted to evaluate whether duration of bDMARD treatment could influence disease activity and HRQoL measures. Mixed linear regression revealed that disease activity (CRP, PtGA, BASDAI, ASDAS), HRQoL (ASQoL and EQ-5D-5L-VAS) and work productivity (WPAI) measures were significantly improved over time compared to baseline, not only in patients who started the bDMARD less than one year before study start but also in patients who received prolonged treatment, independently of radiographic diagnosis, time in study and disease duration (Suppl. Table S2).

Comparison of different bDMARDs on disease activity and HRQoL variables

We next wanted to evaluate whether differences may exist among the four bDMARDs administered over the 12-month follow-up. From a total of 426 patients treated with bDMARDs, 164 (38.5%) received adalimumab, 94 (22.1%) infliximab, 90 (21.1%) etanercept and 48 (11.3%) golimumab.

Mixed linear regression revealed some other differences among the 4 anti-TNF agents for both disease activity and HRQoL measures (Suppl. Table S3). For disease activity variables, no significant difference emerged among the 4 agents, apart from a significant higher value (worse outcome) in PtGA by etanercept *vs.* adalimumab-treated patients (increase of 0.53, 95% CI 0.02–1.05, $p=0.041$) and in BASDAI (etanercept *vs.* infliximab: 0.59, 95% CI 0.07–1.12, $p=0.026$) (Suppl. Table S3). For treatment satisfaction, infliximab emerged as offering superior treatment satisfaction over adalimumab (5.42, 95% CI 0.56-10.28, $p=0.029$), etanercept (7.61, 95% CI 2.0–13.3, $p=0.008$) and golimumab (6.84, 95% CI 0.51–13.2, $p=0.034$). Finally, etanercept showed worse ASQoL values compared with both adalimumab (1.20, 95% CI 0.20–2.20, $p=0.019$) and infliximab (1.62, 95% CI 0.48–2.76, $p=0.005$; Suppl. Table S3).

Discussion

QUASAR is the first observational prospective study conducted in a large population of axSpA patients, representative of patients with AS and nr-axSpA in Italy.

We have previously shown from the baseline analysis of the QUASAR study (17) that patients diagnosed with AS and nr-axSpA share a similar disease burden and therapeutic management profile. The majority of patients (approximately 85%) were treated with bDMARDs and patients treated with bDMARDs compared to other treat-

ments showed improved clinical and HRQoL measures.

The present report extends these findings further, assessing both the change in disease activity, HRQoL, activity impairment and how different treatments may affect these variables over a period of 1 year.

The main findings that have emerged from this follow-up analysis demonstrate that nr-axSpA and AS patients share a similar disease activity profile and HRQoL at baseline and show comparable improvement in disease activity measures (pain, swelling, CRP, PhGA, PtGA, BASDAI, ASDAS), HRQoL (ASQoL and EQ-5D-5L-VAS) and work productivity (WPAI) over a period of 1 year. Mixed-linear regression analysis also confirmed the prolonged use of bDMARDs in achieving improvement in disease activity measures and HRQoL, independently of radiographic diagnosis. Moreover, patients benefitted in a time-dependent manner not only if treated from less than 1 year with marked improvement in all outcome measures but also when undergoing long lasting treatment >3 years.

While previous observational studies have noted differences in demographic and clinical characteristics between nr-axSpA and AS patients (7, 14, 22-24), patients included in the QUASAR study did not share these features. In these studies, AS patients were predominantly male, with higher levels of CRP, BASDAI and ASDAS scores compared to patients who participated in our study. Furthermore, patients included in QUASAR were considerably older and had similar CRP, BASDAI and ASDAS for AS and nr-axSpA patients at baseline.

It is important to note that previous observational studies included patients who had little previous treatment or were naïve to bDMARDs (22-24). As a consequence of the recruitment process in the QUASAR study, patients already receiving medication were not excluded, therefore 496/512 (96.9%) were receiving treatment at baseline, with TNF blockers being the most frequently prescribed regimens (426/512) (83.2%).

At baseline, we observed that a slightly lower proportion of nr-axSpA patients were treated with bDMARDs compared to AS patients (75.8 *vs*. 85%) and this difference may be explained in part by the fairly recent approval of TNF inhibitor use in nr-axSpA in Europe, potentially causing rheumatologists to be less confident in prescribing this treatment for their nr-axSpA patients (25). Corroborating these findings, 78.3% of nr-axSpA and 87.8% of AS patients were treated with bDMARDs in another real-life study in Italy (7).

Mixed linear regression analysis showed that patients treated with bDMARDs had the best overall scores for all indices related to disease activity, function, HRQoL and activity impairment. Lower levels of the ASDAS and BASDAI disease activity indexes observed in the bDMARD group compared to NSAIDs and csDMARDs are likely attributed to a "deeper" effect on the inflammatory process. When this analysis was performed across different bDMARDs, the improvement in outcome variables was independent of radiographic diagnosis. Furthermore, according to EULAR guidelines, NSAIDs are the first line agents for treatment of axial and peripheral manifestations of SpA, accounting for 85 (16%) patients in the QUASAR cohort. It is likely that these patients (as well as those receiving csDMARDs) presented with an active disease, only partially controlled by treatment. A trend toward higher treatment satisfaction, QoL and work productivity with bDMARDs and higher adherence to treatment with bDMARDs (compared to csDMARDs or NSAIDs) was also observed in our patients. It is recognised that routine clinical use of biologics can greatly improve patient QoL (13). However, improvement in QoL measures by bDMARDs *versus* NSAIDs has not always been observed elsewhere, likely attributed to poor adherence by bDMARDs (26, 27). Since the majority of patients in this study were recruited in tertiary care centres this may explain the higher prescription of biologics observed. In this regard, the proportion of patients receiving biologic treatment compared to NSAIDs may not represent the picture of "usual" clinical practice (*e.g*. compared to primary or secondary care hospitals) in these patients. Regardless, data from the REGISPONSERBIO Spanish registry suggest that after the new ASAS classification criteria for SpA (13), biological therapy is being administered earlier than previously in SpA patients and in a higher proportion of patients with nr-axSpA (28). However, this change in prescribing profile has not resulted in an over-treatment since patients do not have a lower disease burden compared to before the new criteria were issued.

Study limitations

There are some potential limitations that need to be highlighted. Weaknesses of observational studies such as the reliability of results and incompleteness of data are recognised (29). Sub-analysis of the effect of different treatments was limited by small sample sizes of some treatment groups. A lack of randomisation may have also introduced selection bias, and the presence of other unmeasured confounders may have also been missed in our analysis. However, we did use mixed linear regression models and corrected for potential confounders, where possible. Although patient compliance was not evaluated in the present study, patient reported treatment satisfaction and MARS-5 questionnaire do provide a useful surrogate marker of treatment compliance.

Patients arrived consecutively and as such in this real-life setting a high proportion (96.9%) were already receiving treatment. Our analysis did not take into consideration the proportion of patients who were naïve or had previous exposure to bDMARDs, since only a small proportion of patients were biologic naïve (n=86; 16.8%).

Conclusion

The findings from this 12-month follow-up of the QUASAR study revealed that disease activity, HRQoL and work impairment were improved over a period of 12 months and this improvement was comparable in patients with nr-axSpA and AS. bDMARDs offered greater benefit over csDMARDs or NSAIDs for all outcome measures, particularly in patients having prolonged treatment. More widespread use of these agents may reduce the burden of these patients and associated healthcare costs.

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In memoriam

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Competing interests

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