Extra-articular manifestations and burden of disease in patients with radiographic and non-radiographic axial spondyloarthritis

Erol K[1], Gok K[1], Cengiz G[1], Kilic G[2], Kilic E[3], Ozgocmen S[4]

ACTA REUMATOL PORT. 2018;43:32-39

ABSTRACT

Objective: Although the prevalence of peripheral and extra-articular disease in ankylosing spondylitis (AS) has been assessed in many studies, data on non-radiographic axial spondyloarthritis (nr-axSpA) is scanty. The aim of this study was first, to compare radiographic-axSpA/AS (r-axSpA/AS) and nr-axSpA concerning peripheral arthritis and extra-articular manifestations (EAMs), and second, to assess potential differences between patient subgroups with or without EAMs regarding disease burden.

Methods: Data was extracted from our single center axSpA database. Patients having at least one of the EAMs (uveitis and/or inflammatory bowel disease (IBD) and/or psoriasis) were compared to those who did not have EAMs. Patients' clinical data including disease activity, functional and psychological status, physical limitations, quality of life (QoL) and magnetic resonance imaging of sacroiliac joints (SIJ MR) were evaluated.

Results: Patients with nr-axSpA (n=193) were younger, had female predominance, better functional and physical status, higher frequency of bone edema in SIJ MR and peripheral arthritis but similar QoL, prevalence of HLA B27 and EAMs compared to r-axSpA/AS (n=352). The prevalence of current or ever uveitis (14.5 vs 15.3%, p=0.791), psoriasis (6.2 vs 5.4%, p=0.689) or IBD (4.1 vs 3.4%, p=0.663) in nr-axSpA and r-axSpA/AS were similar. In both subgroup of patients, EAMs positive and negative patients had similar functional status and QoL, as well as disease activity and laboratory parameters.

Conclusion: Patients with nr-axSpA and r-axSpA/AS have similar prevalence of EAMs and clinical burden of disease. Having EAMs does not have a major influence on clinical parameters and patient reported outcome measures in nr-axSpA and r-axSpA/AS.

Keywords: Spondyloarthritis; Spondylarthropathies; Psoriatic arthritis, Diagnostic imaging; Axial spondyloarthritis; Uveitis; Inflammatory bowel disease.

1. Division of Rheumatology, Department of PMR, ERU Gevher Nesibe Hospital, Kayseri;
2. Division of Rheumatology, Department of PMR, Afyon Kocatepe University, Afyonkarahisar;
3. Rheumatology Clinic, Afyon State Hospital, Afyonkarahisar;
4. Rheumatology, Medical Park Gaziosmanpasa Hospital, Gaziosmanpasa, Istanbul.

INTRODUCTION

Spondyloarthritis (SpA) is a group of diseases classically subdivided into several subtypes including ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, arthritis/spondylitis associated with inflammatory bowel diseases (IBD) and undifferentiated SpA. In this group, AS, a potentially disabling disease, is the prototype of SpA and most common type. The new classification criteria developed by Assessment in Spondyloarthritis International Society (ASAS), suggest terms of axial and peripheral spondyloarthritis. This term covers all spectrum of axial spondyloarthritis (axSpA) including classical AS in one end and non-radiographic axial spondyloarthritis (nr-axSpA) on the other end[1,2]. Non-radiographic axSpA classifies patients with features of SpA and does not necessitate objective signs of inflammation or structural damage on plain sacroiliac radiographs in the clinical arm. It is still subject to debate whether nr-axSpA is a different form of AS, an early form or a look-alike condition[3-5].

Recent studies compared patients with radiographic axial SpA or AS with those with nr-axSpA and documented similar disease characteristics, disease activity, burden of psychological distress and treatment response to TNF inhibitors. However, differences in gender distribution, C-reactive protein (CRP) levels or HLA B27

carriage[6-11] were also found. Although spinal inflammation is the hallmark for SpA, many patients had extra-spinal peripheral manifestations like peripheral arthritis, enthesitis or dactylitis, which are also highly specific features for SpA. Also, extra-articular diseases (uveitis, IBD, psoriasis) are important clinical determinants included in most of the criteria sets for SpA[12-14].

Although the prevalence of peripheral and extra-articular disease in AS has been assessed in many studies, data on nr-axSpA is scanty[15]. Assessment of EAMs in patients with AS and nr-axSpA within well-established cohorts may present important clinical differences, similarities and potential discrepancies, if any, in disease burden between these subgroups. Therefore, our study aimed first, to compare radiographic-axSpA/AS and nr-axSpA concerning peripheral arthritis and EAMs, and second, to assess potential differences between patient subgroups with or without EAMs regarding the disease burden.

PATIENTS AND METHODS

Data were extracted from patients in our single-center (a tertiary center) cohort that has been described elsewhere[8]. Briefly, our cohort included adult patients suffering from chronic low back pain and meeting ASAS criteria for axSpA[7]. Local ethical committee approval was received for this cohort and all patients were informed about the study protocol and gave their written informed consents.

Patients' baseline demographic and clinical data were used in the analysis. Assessments included visual analogue scale of pain (VAS-pain), physician's and patient's global assessment. Patients' quality of life was assessed by short form-36 physical and mental components (SF-36 PCS/MCS) and AS quality of life (ASQoL) questionnaire[16]. Functional status and disease activity were evaluated by Bath ankylosing spondylitis functional index (BASFI) and disease activity index (BASDAI), respectively. The Bath ankylosing spondylitis metrology index (BASMI, on a scale of 0–10) was calculated by anthropometric measurements of cervical rotation, lumbar lateral flexion, tragus-to-wall distance, intermalleolar distance and modified Schober's test. Anxiety and depression were specified by hospital anxiety and depression scale (HADS)[17]. Disability status of the patients was evaluated by health assessment questionnaire-SpA (HAQ-S)[18]. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as well as HLA B27 status were used in the analysis.

Peripheral arthritis was defined as current or ever arthritis of the peripheral joints (defined within 44 joints). Extra-articular manifestations were defined as the current or ever uveitis, and/or current or ever psoriasis, and/or current or ever IBD, diagnosed by an ophthalmologist, dermatologist and gastroenterologist, respectively. The same rheumatologist, who was blind to the laboratory and X-ray examination results, performed physical examination of the patients and queries. Also, hospital records were reviewed by another clinician.

Pelvic X-rays were read by three rheumatologists and the existence of definite sacroiliitis (grade ≥2 bilaterally or grade ≥3 unilaterally according to modified New York criteria) was decided upon consensus. Patients without definite sacroiliitis on pelvic X-ray were defined as nr-axSpA, and patients with definite sacroiliitis on pelvic X-ray were defined as radiographic axSpA or AS (r-axSpA/AS).

Also, MR scans of the sacroiliac joints were evaluated if available. One experienced rheumatologist (S.O.) examined the sacroiliac images and judged the presence or absence of bone edema (BE, yes/no) according to the recommendations of the ASAS/OMERACT MR study group[19].

Statistical analysis was performed using SPSS, version 20.0 (IBM, Armonk, NY, USA) software. Data were expressed as the mean and standard deviations (S.D.). The whole group of patients with axSpA was first categorized into nr-axSpA and r-axSpA/AS, then each group examined within the EAMs (+)ve and (-)ve subgroups. The normality of distribution was analyzed by the Kolmogorov-Smirnov test and 2X2 contingency tables were formed for categorical variables and analyzed by chi-square or Fisher's exact test. The statistical significance of the mean difference between EAMs positive or negative patients with nr-axSpA and r-axSpA/AS was examined using the t-test for normally distributed variables and Mann-Whitney U-test for skewed variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Five hundred forty-five patients with complete records of demographic, clinical and extra-articular manifestations data were included in the analysis. Demographic and clinical data of patients with nr-axSpA and

TABLE I. DEMOGRAPHIC AND CLINICAL DATA IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS (axSpA) INCLUDING NON-RADIOGRAPHIC AXIAL SPA (nr-axSpA) AND RADIOGRAPHIC axSpA/ANKYLOSING SPONDYLITIS (R-AXSPA/AS)

	axSpA (n= 545)		
	nr-axSpA (n=193)	r-axSpA/AS (n=352)	p
Age, mean (S.D.), years	33.65 (9.53)	38.25 (9.81)	<0.0001
Female, n (%)	106 (54.9)	122 (34.7)	<0.0001
Smokers, n (%)	98 (50.8)	220 (62.5)	0.008
BMI, mean (S.D.), kg/m^2	25.46 (5.15)	26.49 (4.70)	0.025
Family history, n (%)	42 (22.2)	97 (28.0)	0.143
Age at diagnosis, mean (S.D.), years	30.84 (10.62)	32.34 (10.55)	0.115
Age at symptom onset, mean (S.D.), years	27.16 (8.36)	27.07 (8.06)	0.902
VAS-pain, (0-10), mean (S.D.)	4.64 (2.70)	4.57 (4.00)	0.843
PtGA, (0-10), mean (S.D.)	4.53 (2.51)	4.58 (2.67)	0.849
PGA, (0-10), mean (S.D.)	3.57 (1.87)	3.69 (2.17)	0.531
MR sacroiliitis, (n=168 vs 253), n (%)	147 (87.5)	170 (67.2)	<0.0001
ESR, mean (S.D.), (mm/h)	19.39 (18.29)	21.39 (19.62)	0.252
CRP, mean (S.D.), (mg/l)	12.53 (18.57)	15.12 (21.35)	0.169
HLA B27 positive, (n=164 vs 255), n (%)	95 (57.9)	169 (66.3)	0.084
ASDAS-CRP, mean (S.D.)	2.70 (0.98)	2.85 (1.06)	0.143
BASDAI, (0-10), mean (S.D.)	3.97 (2.18)	3.90 (2.41)	0.714
BASFI, (0-10), mean (S.D.)	2.38 (2.17)	3.00 (2.49)	0.005
BASMI, (0-10), mean (S.D.)	1.66 (1.41)	2.63 (1.84)	<0.0001
HADS- anxiety, mean (S.D.)	7.30 (4.38)	7.22 (4.30)	0.854
HADS- depression, mean (S.D.)	6.22 (3.83)	6.80 (4.24)	0.134
SF-36/PCS, (0-100), mean (S.D.)	48.73 (22.34)	47.84 (23.46)	0.708
SF-36/MCS, (0-100), mean (S.D.)	54.14 (21.91)	52.18 (22.58)	0.398
ASQoL, mean (S.D.)	8.01 (7.43)	8.21 (5.49)	0.730
HAQ-S, mean (S.D.)	0.65 (0.53)	0.69 (0.56)	0.472
EAM positive, n (%)	42 (21.8)	74 (21)	0.840
Uveitis, n (%)	28 (14.5)	54 (15.3)	0.791
PsO, n (%)	12 (6.2)	19 (5.4)	0.689
IBD, n (%)	8 (4.1)	12 (3.4)	0.663
Peripheral arthritis, n (%)	47 (24.4)	60 (17)	0.040

BMI, body mass index; VAS, visual analogue scale; PtGA, patient's global assessment; PGA, physician's global assessment; MR, magnetic resonance imaging; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath AS disease activity index; BASFI, Bath AS functional index; HADS, hospital anxiety and depression scale; SF-36, short-form 36; ASQoL, AS quality of life; HAQ-S, health assessment questionnaire-spondyloarthritis; EAM, extra-articular manifestation; PsO, psoriasis; IBD, inflammatory bowel disease

r-axSpA/AS are shown in Table I. One hundred ninety-three patients who did not meet radiographic criteria for sacroiliitis were classified as nr-axSpA and 32 (16.6%) of these patients met only the clinical arm of the ASAS criteria for axSpA. Patients who met radiographic criteria for sacroiliitis were classified as r-axSpA/AS (n=352). Patients with nr-axSpA were younger and had lower values of BMI than patients with r-axSpA/AS, however age at symptom onset and diagnosis and HLA B27 prevalence were similar. Patients in the r-axSpA/AS group had male predominance, whereas nr-axSpA had female predominance. Patients with nr-axSpA had slightly higher prevalence of peripheral arthritis but similar prevalence of EAMs (Table I). Interestingly, prevalence of smokers (current or ex-smokers) in the r-axSpA/AS group was signifi-

TABLE II. DEMOGRAPHIC AND CLINICAL DATA IN EXTRA-ARTICULAR MANIFESTATIONS POSITIVE [EAM (+)VE] AND NEGATIVE [EAMS (-)VE] PATIENTS WITH nr-axSpA

	nr-axSpA (n= 193)		
	EAM (+)ve (n=42)	EAM (–)ve (n=151)	p
Age, mean (S.D.), years	33.83 (9.37)	33.60 (9.61)	0.887
Female, n (%)	23 (54.8)	83 (54.9)	0.981
Smokers, n (%)	20 (47.6)	78 (51.7)	0.643
BMI, mean (S.D.), kg/m^2	25.19 (5.44)	25.53 (5.09)	0.725
Family history, n (%)	12 (29.3)	30 (20.3)	0.220
Age at diagnosis, mean (S.D.), years	30.26 (10.63)	31.00 (10.65)	0.691
Age at symptom onset, mean (S.D.), years	26.88 (8.34)	27.24 (8.40)	0.806
VAS-pain, (0-10), mean (S.D.)	4.51 (2.99)	4.67 (2.63)	0.738
PtGA, (0-10), mean (S.D.)	4.87 (2.80)	4.44 (2.42)	0.323
PGA, (0-10), mean (S.D.)	3.94 (2.11)	3.46 (1.79)	0.145
MR sacroiliitis, (n=36 vs 132), n (%)	31 (86.1)	116 (87.9)	0.483
ESR, mean (S.D.), (mm/h)	18.62 (15.24)	19.59 (19.05)	0.767
CRP, mean (S.D.) (mg/l)	11.50 (20.26)	12.79 (18.18)	0.707
HLA B27 positive, (n=33 vs 131) n (%)	21 (63.6)	74 (56.5)	0.457
ASDAS-CRP, mean(S.D.)	2.82 (1.15)	2.68 (0.93)	0.436
BASDAI, (0-10), mean (S.D.)	4.26 (2.63)	3.89 (2.05)	0.342
BASFI, (0-10), mean (S.D.)	2.16 (2.01)	2.44 (2.21)	0.474
BASMI, (0-10), mean (S.D.)	1.52 (1.34)	1.69 (1.43)	0.588
HADS- anxiety, mean (S.D.)	8.63 (4.84)	6.88 (4.15)	0.024
HADS- depression, mean (S.D.)	7.05 (4.35)	5.96 (3.64)	0.114
SF-36/PCS, (0-100), mean (S.D.)	48.84 (20.71)	48.70 (22.92)	0.974
SF-36/MCS, (0-100), mean (S.D.)	53.37 (23.99)	54.38 (21.33)	0.818
ASQoL, mean (S.D.)	7.93 (5.14)	8.04 (7.97)	0.935
HAQ-S, mean (S.D.)	0.70 (0.57)	0.64 (0.52)	0.563
Peripheral arthritis, n (%)	12 (28.6)	35 (23.2)	0.471

BMI, body mass index; VAS, visual analogue scale; PtGA, patient's global assessment; PGA, physician's global assessment; MR, magnetic resonance imaging; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath AS disease activity index; BASFI, Bath AS functional index; HADS, hospital anxiety and depression scale; SF-36, short-form 36; ASQoL, Ankylosing spondylitis quality of life; HAQ-S, health assessment questionnaire-spondyloarthritis

cantly higher than in the nr-axSpA group. Patients with r-axSpA/AS and nr-axSpA had similar values in most clinical outcome measures, except for BASMI and BASFI which were poorer in patients with r-axSpA/AS (Table I). Magnetic resonance imaging of the sacroiliac joints was available in 168 patients with nr-axSpA and 253 patients with r-axSpA/AS, and bone edema (unilateral or bilateral) was significantly more prevalent in nr-axSpA compared to r-axSpA/AS (p<0.0001). In biologic naïve patients, MR of the sacroiliac joints was available in 151 patients with nr-axSpA and 195 patients with r-axSpA/AS, and bone edema (unilateral or bilateral) was significantly more prevalent in nr-axSpA compared to r-axSpA/AS (p<0.0001).

Patients with nr-axSpA and r-axSpA/AS were also compared regarding the current treatments and TNF inhibitor use was significantly higher in r-axSpA/AS compared to nr-axSpA (22.7% vs 11.9%, p=0.002, respectively). Data were analyzed regarding differences between nr-axSpA and r-axSpA/AS patients who were naïve for TNF inhibitors by excluding patients under treatment with TNF inhibitors. Analysis of these biologic naïve patients (n=442) revealed the same significant differences in the same parameters (nr-axSpA vs r-axSpA/AS) with respect to the former analysis including whole group of patients (data not shown). In the whole group of axSpA (n=545), 116 (21.2%) were EAM (+)ve (had at least one EAM of uveitis, psoriasis

TABLE III. DEMOGRAPHIC AND CLINICAL DATA IN EXTRA-ARTICULAR MANIFESTATIONS POSITIVE [EAM (+)VE] AND NEGATIVE [EAMS (-)VE] PATIENTS WITH r-axSpA/AS

	r-axSpA/AS (n=352)		
	EAM (+)ve (n=74)	EAM (–)ve (n=278)	p
Age, mean (S.D.), years	38.85 (9.77)	38.09 (9.83)	0.552
Female, n (%)	23 (31.1)	99 (35.6)	0.467
Smokers, n (%)	44 (59.5)	176 (63.3)	0.543
BMI, mean (S.D.), kg/m^2	26.52 (4.08)	26.48 (4.86)	0.955
Family history, n (%)	19 (26.8)	78 (28.4)	0.789
Age at diagnosis, mean (S.D.), years	30.46 (10.80)	32.83 (10.45)	0.085
Age at symptom onset, mean (S.D.), years	25.79 (7.15)	27.41 (8.27)	0.130
VAS-pain, (0-10), mean (S.D.)	4.53 (3.02)	4.58 (4.23)	0.921
PtGA, (0-10), mean (S.D.)	4.61 (2.75)	4.57 (2.65)	0.921
PGA, (0-10), mean (S.D.)	3.70 (2.19)	3.69 (2.17)	0.972
MR sacroiliitis, (n=54 vs 199), n (%)	33 (61.1)	137 (68.8)	0.284
ESR, mean (S.D.), (mm/h)	23.15 (19.22)	20.95 (19.74)	0.410
CRP, mean (S.D.), (mg/l)	15.72 (19.32)	14.97 (21.87)	0.796
HLA B27 positive, (n=50 vs 205) n (%)	40 (80)	129 (62.9)	0.022
ASDAS-CRP, mean (S.D.)	2.89 (1.17)	2.83 (1.04)	0.728
BASDAI, (0-10), mean (S.D.)	3.88 (2.56)	3.90 (2.38)	0.938
BASFI, (0-10), mean (S.D.)	3.16 (2.68)	2.96 (2.44)	0.542
BASMI, (0-10), mean (S.D.)	2.91 (1.64)	2.56 (1.89)	0.211
HADS- anxiety, mean (S.D.)	6.09 (4.03)	7.53 (4.33)	0.013
HADS- depression, mean (S.D.)	6.41 (4.17)	6.91 (4.26)	0.380
SF-36/PCS, (0-100), mean (S.D.)	48.55 (23.83)	47.65 (23.41)	0.793
SF-36/MCS, (0-100), mean (S.D.)	53.55 (24.05)	51.82 (22.23)	0.598
ASQoL, mean (S.D.)	7.57 (5.65)	8.38 (5.45)	0.260
HAQ-S, mean (S.D.)	0.72 (0.63)	0.69 (0.55)	0.713
Peripheral arthritis, n (%)	21 (28.4)	39 (14)	0.004

BMI, body mass index; VAS, visual analogue scale; PtGA, patient's global assessment; PGA, physician's global assessment; MR, magnetic resonance imaging; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath AS disease activity index; BASFI, Bath AS functional index; HADS, hospital anxiety and depression scale; SF-36, short-form 36; ASQoL, Ankylosing spondylitis quality of life; HAQ-S, health assessment questionnaire-spondyloarthritis

or IBD) and patients with EAMs had significantly higher prevalence of HLA B27 (73.5% vs 60.5%, p=0.028) and peripheral arthritis (28.4% vs 17.4%, p=0.008) compared to patients without EAMs. Other study parameters were quite similar between EAMs positive and negative patients with axSpA (data not shown).

Table II shows that nearly all of the clinical and outcome measures were quite similar between EAM (+)ve and EAM (-)ve patients with nr-axSpA, except for HAD-anxiety scores. Table III shows results in patients with r-axSpA/AS accordind to EAMs. EAM (+)ve patients with r-axSpA/AS tend to have higher prevalence of HLA B27 and peripheral arthritis compared to patients without EAMs (Table III).

DISCUSSION

In this study, we showed that patients with nr-axSpA and r-axSpA/AS have similarities regarding EAMs and clinical burden, however had several differences regarding demographic and functional measures (humanistic burden). We demonstrated for the first time that having EAMs (at least one of the manifestations of uveitis, psoriasis or IBD) do not promote major differences in the clinical and patient reported outcome variables in patients with nr-axSpA and r-axSpA/AS. In r-axSpA/AS patients with EAMs tended to have more prevalent HLA B27 and peripheral arthritis.

Our results are largely in accordance with the pre-

vious studies underscoring similarities between nr-axSpA and AS regarding the burden of disease and EAMs[15,20-22]. The female predominance in patients with nr-axSpA, which was reported by others, was confirmed by our observational data. Besides, we showed similar prevalence of HLA B27 between nr-axSpA and r-axSpA/AS, but with globally lower prevalence which is peculiar to our patient population. Previous cohorts showed similar HLA B27 prevalence varying between 74.7% and 89.1% in nr-axSpA and AS[6,7,23]. While estimating the prevalence of HLA B27, the percentage of patients meeting the clinical and imaging arms is also important, since taking the majority of the group from the clinical arm may cause an overestimation in HLA B27. In a recent abstract, the authors separately analyzed patients (Esperanza cohort) with nr-axSpA and AS in the imaging arm only and underscored similar prevalence of HLA B27 (58.5% in nr-axSpA imaging arm vs 67.6% in AS)[24]. Patient numbers in the clinical arm was very small in our study and the reported prevalence in the Esperanza cohort was quite similar to the prevalence found in our patient population. Indeed, HLA B27 prevalence in Turkish patients with AS has been previously reported to be lower (70%) than in other populations[25]. Also, relatively lower but not statistically significantly different prevalence of HLA B27 in Turkish patients with AS (68.3%) and nr-axSpA (46.3%) has been previously reported as an abstract[26]. The relatively lower prevalence may be related to the ethnic and geographical differences.

The distribution of clinical features, including extra-articular features like psoriasis, uveitis andIBD, was quite similar between nr-axSPA and AS in the previous cohorts[6,7,9,21]. In a recent meta-analysis, de Winter *et al.* analyzed data from the published cohorts to assess the prevalence of peripheral and extra-articular disease in patents with AS vs nr-axSpA [15]. Eight studies were systematically reviewed in this meta-analysis and the authors concluded a similar prevalence of arthritis, enthesitis, dactylitis as well as psoriasis and IBD in AS vs nr-axSpA. On the other hand, a higher pooled prevalence of uveitis was reported in AS (23%) vs nr-axSpA (15.9%)[15]. The prevalence of psoriasis, IBD and uveitis in our study was in accordance with the reported pooled prevalence in this meta-analysis. Conversely, our patients with nr-axSpA had significantly more prevalent peripheral arthritis compared to patients with r-axSpA/AS. Also, the prevalence of uveitis has been shown to be related with the disease duration[27-29]. Patients with r-axSpA/AS had relatively higher symptom duration in most of the studies and this may be one of the explanations for higher prevalence of uveitis compared to nr-axSpA. Our study focused on extra-articular disease and did not analyze extra-articular manifestations like dactylitis and enthesitis. Indeed, dactylitis and enthesitis may coincide with extra-articular disease like psoriasis and may be analyzed in future research.

Data on the burden of disease in nr-axSpA and AS is an interesting field of research and continues to accumulate. With the approval of TNF inhibitors for the treatment of nr-axSpA by the European Medicines Agency (EMA) and the issue of recommendations for their use in patients with nr-axSpA, the burden of nr-axSpA in comparison to AS gained attention[30,31]. Although the clinical and humanistic burden (domestic activity, work productivity, disability and HRQoL) of nr-axSpA and AS has been compared in some cohorts, data on economic burden, health-care utilization and costs is sparse[20].

Similar physical function, assessed by BASFI, has been reported in nr-axSpA and AS[9,32,33]. On the other hand, higher functional loss has also been reported in AS compared to nr-axSpA, similar to our results[7,23,34,35]. Patients with r-axSpA or AS had more physical limitations, assessed by BASMI, than patients with nr--axSpA[7,9,33-35]. Indeed, better functional status is not surprising in patients with nr-axSpA in comparison to AS, since patients with nr-axSpA had generally shorter symptom duration and possibly less structural damage in axial skeleton, which may explain this difference. Our results also revealed that having EAMs did not have a major contribution to functional loss and physical limitation.

Studies on the existence and extent of spinal inflammation in nr-axSpA *vs* AS are not conclusive[12,32,35,36]. In this study, we could document acute inflammation by means of BME detected in the MR scans of SIJs. Significantly, higher number of patients with nr-axSpA had BME in the SIJ MR compared to r-axSpA/AS. Ankylosis and termination of the inflammatory phase with the longstanding disease may be one explanation. Having or not having EAMs did not have an effect on the existence of BME in the SIJ MR in both groups. We could not assess spinal inflammation on MR or structural damage in the axial skeleton, which is a limitation of the study. Treatment with TNF inhibitors also had an effect on the inflammatory signs on MR of the spine and SIJs. To eradicate this effect, we analyzed patients excluding TNF inhibitor users in both groups.

The analysis of the biologic-naïve patients revealed similar results: a larger number of patients with nr-axSpA had BME on MR scans of the SIJ than patients with r-axSPA/AS.

In this study, we could only compare patients with at least one of the EAMs and could not assess each EAM separately, because of the small numbers when subcategorized. A group of researchers have compared spondylitis patients associated with psoriasis or IBD versus AS and found more severe axial involvement in AS and similar functional capacity, disease activity and QoL[37]. Likewise, patients with axial psoriatic arthritis have been compared with non-psoriatic axial SpA (including patients with nr-axSpA), suggesting that patients with axial PsA had poorer physical and social functioning, higher prevalence of peripheral arthritis and lower prevalence of HLA B27 compared to non-psoriatic axial SpA[38].

Regarding the classification of patients with nr-axSpA or r-axSpA, we categorized X-rays based on the agreement of three rheumatologist in order to reduce bias. There is a continuing discussion on the potential influence of X-ray interpretation because of the poor reproducibility and inconsistency of structural damage assessment among rheumatologists[39]. In addition, we did not accept an EAM as valid unless confirmed by a physician in the related discipline.

In conclusion, patients with nr-axSpA are more likely to be female and have peripheral arthritis, better physical functions and mobility; however, they have similar prevalence of EAMs and burden of disease in regards to the level of disease activity and quality of life. Having EAMs does not have a major influence on clinical parameters and patient reported outcome measures in nr-axSpA and r-axSpA/AS.

CORRESPONDENCE TO

Ozgocmen S
Medicalpark Gaziosmanpasa Hospital, Rheumatology,
Gaziosmanpasa, 34245
E-mail: sozgocmen@hotmail.com

REFERENCES

1. Deodhar A, Reveille JD, van den Bosch F, et al. The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the Assessment of SpondyloArthritis international Society in response to the US Food and Drug Administration's comments and concerns. Arthritis Rheumatol 2014; 66(10): 2649-2656.
2. Ozgocmen S, Khan MA. Current concept of spondyloarthritis: special emphasis on early referral and diagnosis. Curr Rheumatol Rep 2012; 14(5): 409-414.
3. Sieper J, van der Heijde D. Review: Nonradiographic axial spondyloarthritis: new definition of an old disease? Arthritis Rheum 2013; 65(3): 543-551.
4. van der Linden S, Akkoc N, Brown MA, Robinson PC, Khan MA. The ASAS Criteria for Axial Spondyloarthritis: Strengths, Weaknesses, and Proposals for a Way Forward. Curr Rheumatol Rep 2015; 17(9): 62.
5. Molto A, Etcheto A, van der Heijde D, et al. Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. Ann Rheum Dis 2016; 75(6): 1016-1023.
6. Kiltz U, Baraliakos X, Karakostas P, et al. Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? Arthritis Care Res (Hoboken) 2012; 64(9): 1415-1422.
7. Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum 2009; 60(3): 717--727.
8. Kilic E, Kilic G, Akgul O, Ozgocmen S. Discriminant validity of the Ankylosing Spondylitis Disease Activity Score (ASDAS) in patients with non-radiographic axial spondyloarthritis and ankylosing spondylitis: a cohort study. Rheumatol Int 2015; 35(6): 981-989.
9. Ciurea A, Scherer A, Exer P, et al. Tumor necrosis factor alpha inhibition in radiographic and nonradiographic axial spondyloarthritis: results from a large observational cohort. Arthritis Rheum 2013; 65(12): 3096-3106.
10. Song IH, Weiss A, Hermann KG, et al. Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. Ann Rheum Dis 2013; 72(6): 823-825.
11. Kilic G, Kilic E, Ozgocmen S. Relationship between psychiatric status, self-reported outcome measures, and clinical parameters in axial spondyloarthritis. Medicine (Baltimore) 2014; 93(29): e337.
12. Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. Rev Rhum Mal Osteoartic 1990; 57(2): 85-89.
13. Dougados M, van der Linden S, Juhlin R, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991; 34(10): 1218-1227.
14. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009; 68(6): 777-783.
15. de Winter JJ, van Mens LJ, van der Heijde D, Landewe R, Baeten DL. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. Arthritis Res Ther 2016; 18: 196.
16. Duruoz MT, Doward L, Turan Y, et al. Translation and validation of the Turkish version of the Ankylosing Spondylitis Quality of Life (ASQOL) questionnaire. Rheumatol Int 2013; 33(11): 2717-2722.
17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67(6): 361-370.
18. Daltroy LH, Larson MG, Roberts NW, Liang MH. A modification of the health assessment questionnaire for the spondyloarthropathies. J Rheumatol 1990; 17(7): 946-950.
19. Rudwaleit M, Jurik AG, Hermann KG, et al. Defining active

sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis 2009; 68(10): 1520-1527.
20. Sieper J, Hu X, Black CM, Grootscholten K, van den Broek RW, Kachroo S. Systematic review of clinical, humanistic, and economic outcome comparisons between radiographic and non-radiographic axial spondyloarthritis. Semin Arthritis Rheum 2017; 46(6): 746-753.
21. Boonen A, Sieper J, van der Heijde D, et al. The burden of non-radiographic axial spondyloarthritis. Semin Arthritis Rheum 2015; 44(5): 556-562.
22. Sieper J, Holbrook T, Black CM, Wood R, Hu X, Kachroo S. Burden of illness associated with non-radiographic axial spondyloarthritis: a multiperspective European cross-sectional observational study. Clin Exp Rheumatol 2016; 34(6): 975-983.
23. Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014; 73(1): 39-47.
24. Hernández-Sanz A, Navarro-Compán V, Fernández-Carballido C, Montilla-Morales C, Mulero J, De Miguel E. Ankylosing spondylitis and non-radiographic axial spondyloarthritis : The same syndrome or different diseases? Analysis from Esperanza cohort. Arthritis Rheum 2014; 66(Suppl): 2604.
25. Gunal EK, Sarvan FO, Kamali S, et al. Low frequency of HLA-B27 in ankylosing spondylitis patients from Turkey. Joint Bone Spine 2008; 75(3): 299-302.
26. Solmaz D, Akar S, Sari I, Cetin P, Onen F, Akkoc N. Comparison of the two subtypes of axial spondyloarthritis patients fulfilling the imaging arm based on radiographic and MRI findings. Arthritis Rheum 2013; 65(Suppl 10): 2473.
27. Essers I, Ramiro S, Stolwijk C, et al. Characteristics associated with the presence and development of extra-articular manifestations in ankylosing spondylitis: 12-year results from OASIS. Rheumatology (Oxford) 2015; 54(4): 633-640.
28. Stolwijk C, Essers I, van Tubergen A, et al. The epidemiology of extra-articular manifestations in ankylosing spondylitis: a population-based matched cohort study. Ann Rheum Dis 2015; 74(7): 1373-1378.
29. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis 2015; 74(1): 65-73.
30. Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis. Arthritis Rheumatol 2016; 68(2): 282-298.
31. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017; 76(6): 978-991.
32. Kiltz U, Baraliakos X, Karakostas P, et al. The degree of spinal inflammation is similar in patients with axial spondyloarthritis who report high or low levels of disease activity: a cohort study. Ann Rheum Dis 2012; 71(7): 1207-1211.
33. Malaviya AN, Kalyani A, Rawat R, Gogia SB. Comparison of patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) from a single rheumatology clinic in New Delhi. Int J Rheum Dis 2015; 18(7): 736-741.
34. Lubrano E, Perrotta FM, Marchesoni A, et al. Remission in non-radiographic axial spondyloarthritis treated with anti-tumor necrosis factor-alpha drugs: an Italian multicenter study. J Rheumatol 2015; 42(2): 258-263.
35. Poddubnyy D, Haibel H, Braun J, Rudwaleit M, Sieper J. Brief Report: Clinical Course Over Two Years in Patients With Early Nonradiographic Axial Spondyloarthritis and Patients With Ankylosing Spondylitis Not Treated With Tumor Necrosis Factor Blockers: Results From the German Spondyloarthritis Inception Cohort. Arthritis Rheumatol 2015; 67(9): 2369-2375.
36. Weber U, Pedersen SJ, Zubler V, et al. Fat infiltration on magnetic resonance imaging of the sacroiliac joints has limited diagnostic utility in nonradiographic axial spondyloarthritis. J Rheumatol 2014; 41(1): 75-83.
37. Perez Alamino R, Maldonado Cocco JA, Citera G, et al. Differential features between primary ankylosing spondylitis and spondylitis associated with psoriasis and inflammatory bowel disease. J Rheumatol 2011; 38(8): 1656-1660.
38. Ozgocmen S, Cengiz G, Erol K, et al. Comparison of clinical features in patients with psoriatic and non-psoriatic spondylitis Clin Exp Rheumatol 2016; 34(4): 760.
39. Deodhar A, Strand V, Kay J, Braun J. The term 'non-radiographic axial spondyloarthritis' is much more important to classify than to diagnose patients with axial spondyloarthritis. Ann Rheum Dis 2016; 75(5): 791-794.