ORIGINAL ARTICLE

Characterization of Patients With Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis in the US-Based Corrona Registry

PHILIP J. MEASE,[1] DÉSIRÉE van der HEIJDE,[2] CHITRA KARKI,[3] JACQUELINE B. PALMER,[4]
MEI LIU,[3] RENGANAYAKI PANDURENGAN,[3] YUJIN PARK,[4] AND JEFFREY D. GREENBERG[5]

Objective. To describe the characteristics of patients with ankylosing spondylitis (AS) and patients with nonradiographic axial spondyloarthritis (SpA) in the US.
Methods. Demographics, clinical characteristics, patient-reported outcomes, and treatment characteristics of patients with AS and those with nonradiographic axial SpA were assessed at the time of enrollment in the Corrona Psoriatic Arthritis/Spondyloarthritis Registry. Patients with AS were defined as those who fulfilled the 1984 modified New York criteria for AS; patients with nonradiographic axial SpA were defined as all other patients with axial SpA who did not fulfill the radiology criterion.
Results. Of the 407 patients with a diagnosis of axial SpA who were included in this study, 310 had AS, and 97 had nonradiographic axial SpA. Although patients with nonradiographic axial SpA were younger and showed a trend toward a shorter symptom duration, the nonradiographic axial SpA and AS groups shared a similar disease burden, as reflected by comparisons of disease activity and function, quality of life, pain, fatigue, job absenteeism, and loss of work productivity (all $P > 0.05$). The proportions of patients with nonradiographic axial SpA and patients with AS who received prior biologic disease-modifying drugs (DMARDs) (74.2% and 64.8%, respectively) or were currently receiving biologic DMARDs (63.9% and 61.3%, respectively) were also similar ($P > 0.05$).
Conclusion. This was the first nationwide study to characterize patients with AS and nonradiographic axial SpA in the US. Consistent with studies published outside of the US, this study showed that patients with nonradiographic axial SpA and patients with AS shared a comparable degree of disease burden and had similar treatment patterns in clinical practice.

INTRODUCTION

Axial spondyloarthritis (SpA) is a chronic inflammatory rheumatic disease that primarily affects the axial skeleton and frequently affects the peripheral joints and entheses (1), with an estimated prevalence in the US of 0.9–1.4% (2–4).

The diagnosis of axial SpA encompasses patients in whom radiographic sacroiliitis (radiographic axial SpA; also commonly referred to as ankylosing spondylitis [AS]) has already developed and patients without any evidence of radiographic structural damage (nonradiographic axial SpA). Structural damage may or may not eventually develop in patients with

Significance & Innovations

- In this analysis of patients with axial spondyloarthritis in the US-based Corrona Psoriatic Arthritis/Spondyloarthritis Registry, we observed no differences between patients with ankylosing spondylitis and patients with nonradiographic axial spondyloarthritis regarding prior/current biologic disease-modifying antirheumatic drug use, disease activity and function, quality of life, pain, fatigue, or job absenteeism and loss of work productivity.
- Despite some differences in patient and clinical characteristics, other similarities in measures of disease activity, disease function, and patient-reported outcomes between patients with ankylosing spondylitis and those with nonradiographic axial spondyloarthritis suggest that these subgroups have a comparable and significant disease burden and are managed similarly in clinical practice.

nonradiographic axial SpA. However, radiographic sacroiliitis may take years to develop, if it develops at all, which complicates identification and delays management of patients who may have earlier stages of disease but do not present with evident signs of damage in the sacroiliac joints.

The Assessment of SpondyloArthritis international Society (ASAS) recently developed classification criteria to include patients who have radiographic sacroiliitis and who largely will also fulfill the 1984 modified New York criteria for AS, as well as patients with nonradiographic sacroiliitis (i.e., those who do not have sacroiliitis on radiographic images but may have evidence of sacroiliitis by magnetic resonance imaging [MRI]), or the presence of HLA–B27 plus ≥2 other clinical features) (5).

Although understanding of AS itself has increased significantly over the past 2 decades, less information is available regarding characteristics of nonradiographic axial SpA. Patients with nonradiographic axial SpA exhibit a substantial disease burden (6–8), although the clinical profile of these patients is still under investigation. Aside from the presence of radiographic sacroiliitis, AS has been shown to be associated with a higher prevalence of men, elevated levels of markers of inflammation, and decreased measures of spinal mobility compared with nonradiographic axial SpA (9–18). Despite these differences, previous studies have also shown that patients with AS and patients with nonradiographic axial SpA were similar regarding HLA–B27 positivity, signs of peripheral inflammation, disease activity indices, and patient-reported outcomes (9–11,13–18).

Cohort studies have demonstrated that acute-phase reactants (e.g., C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]), and especially a disease activity patient-reported outcome score incorporating the CRP or ESR (i.e., the Ankylosing Spondylitis Disease Activity Score [ASDAS]), were associated with spinal radiographic progression (19–21); however, few data are available to determine whether and which patients with nonradiographic axial SpA will develop structural

changes in the sacroiliac joints and experience such progression (19,22). Although the similarities and differences between nonradiographic axial SpA and AS may suggest that, for some patients, these classifications represent early and later stages of axial SpA, it is not known whether this distinction is clinically relevant or warrants different treatment strategies.

The goals of treatment of patients with axial SpA are to reduce symptoms of pain, stiffness, and fatigue; maintain spinal flexibility and normal posture; reduce functional limitations; maintain work productivity; and decrease associated extraarticular manifestations (e.g., uveitis) and comorbidities (e.g., spinal fractures and cardiovascular damage) (23,24). Treatment of nonradiographic axial SpA was first acknowledged in the 2010 update of the ASAS/European League Against Rheumatism (EULAR) recommendations for the management of AS (25). These recommendations were updated in 2016 to cover the entire spectrum of axial SpA (24). The 2016 update recommends that treatment with biologic disease-modifying antirheumatic drugs (DMARDs), including anti–interleukin-17 inhibitors and tumor necrosis factor (TNF) treatment should be considered for patients with persistently high disease activity despite receiving conventional treatments, including nonsteroidal antiinflammatory drugs (NSAIDs); current practice is to start treatment with a TNF inhibitor (24).

In 2015, the American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) collaborated to provide a guideline for the treatment and management of patients with AS and nonradiographic axial SpA (23). The guideline also recommends treating both patients with AS and patients with nonradiographic axial SpA with NSAIDs and TNF inhibitors if the patient presents with active disease despite treatment with NSAIDs. The use of conventional synthetic DMARDs (csDMARDs) is not recommended in patients with axial SpA without peripheral arthritis.

Even with the emergence of international guidelines recommending biologic DMARD treatment in all patients with axial SpA (not just those with AS), only 4 TNF inhibitors (adalimumab, certolizumab pegol, etanercept, and golimumab) are approved in the European Union for the treatment of patients with nonradiographic axial SpA who have objective signs of inflammation as indicated by an elevated CRP level and/or evidence of active sacroiliitis on MRI (26–29). Currently, no biologic DMARDs are approved for the treatment of nonradiographic axial SpA in the US. The treatment patterns in patients with axial SpA, including those in the nonradiographic axial SpA and AS subgroups, in real-world settings are still unknown, particularly in the US.

Although data from clinical trials are useful to understand the efficacy of medications in a well-characterized, homogeneous disease population, real-world data from registries are helpful to understand the disease characteristics of patients realistically seen in clinical practice. A few cohort and observational studies have described the differences and similarities between patients with AS and patients with nonradiographic axial SpA; however, most of those studies were conducted outside of the US (8–18).

The objective of this descriptive cross-sectional study was to provide a nationwide clinical cohort perspective from the US through examination of the demographic, clinical, and treatment characteristics of patients with AS and patients with nonradiographic axial SpA at the time of enrollment into a US-based registry.

PATIENTS AND METHODS

Study population. The Corrona Psoriatric Arthritis (PsA)/SpA Registry is a large, independent, prospective, observational cohort of patients in whom PsA and SpA were diagnosed by a rheumatologist. The Corrona PsA/SpA Registry database includes information about 10,174 patient visits, with a mean duration of patient follow-up of 2.8 years (median 3.1 years). As of November 2017, data for 2,445 patients with PsA/SpA had been collected from 32 private and academic practice sites across 21 states in the US, with 42 rheumatologists participating. The current study included all patients ages ≥18 years with a diagnosis of axial SpA who were enrolled in the Corrona PsA/SpA Registry as of July 2015.

Patients were included in this analysis if they fulfilled the ASAS classification criteria (5). Briefly, patients should have had back pain for ≥3 months and an age at onset of <45 years and were required to have sacroiliitis on imaging and ≥1 SpA feature or be HLA–B27–positive and have ≥2 other SpA features. The presence of sacroiliitis on imaging was defined as either active (acute) inflammation on MRI that is highly suggestive of sacroiliitis associated with SpA or definite radiographic sacroiliitis according to the 1984 modified New York criteria (30). SpA features that were assessed included presence of inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, and Crohn's disease/colitis; good response to NSAIDs; family history of SpA; HLA–B27 positivity; and elevated CRP levels.

The population of patients with axial SpA was further divided into subgroups of patients with AS and patients with nonradiographic axial SpA. The definition of AS was based on the 1984 modified New York criteria for AS as applied by the investigator, which is the radiology criterion (sacroiliitis grade ≥2 bilaterally or grade ≥3 unilaterally) in association with ≥1 clinical criterion (low back pain and stiffness for ≥3 months that improve with exercise but are not relieved by rest, and/or limitation of motion of the lumbar spine in both the sagittal and frontal planes [30]). Patients with nonradiographic axial SpA were defined as all others with axial SpA who did not fulfill the radiology criterion.

The Corrona PsA/SpA Registry and this analysis were approved by local institutional review boards at participating academic sites and a central institutional review board (the New England Institutional Review Board) for private practice sites. All patients provided written informed consent.

Outcomes and assessments. Data were collected using questionnaires from treating rheumatologists and patients at office visits, approximately every 6 months. All assessments, including demographics, clinical characteristics, patient-reported outcomes, and medication history, were collected at baseline (i.e., time of enrollment in the Registry). Data were collected on demographics (e.g., age, symptom duration [from onset], sex, race, body mass index [BMI]), history of comorbidities, family history, and prior and current medication (csDMARDs, biologic DMARDs, and prednisone). In addition, data on clinical features were collected (e.g., enthesitis, using the Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index; dactylitis; and tender and swollen joint counts), laboratory measurements (e.g., CRP level and ESR), disease activity measures (e.g., Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] and Ankylosing Spondylitis Disease Activity Score using the CRP [ASDAS]), physical function (Bath Ankylosing Spondylitis Functional Index [BASFI], Health Assessment Questionnaire for the Spondyloarthropathies [HAQ-S], spinal mobility measures [occiput-to-wall distance and lateral lumbar flexion]), and a number of patient-reported outcomes (e.g., pain, fatigue, morning stiffness, quality of life using the EuroQol 5-domain questionnaire [EQ-5D], and the Work Productivity and Activity Impairment questionnaire).

Statistical analysis. Descriptive analyses of patient demographics, clinical characteristics, patient-reported outcomes, and medication history were conducted for the entire Corrona axial SpA population at baseline and stratified according to patients with AS and those with nonradiographic axial SpA. Categorical variables were summarized using frequency counts and percentages. Continuous variables were summarized as the mean ± SD. Normality tests were performed for all continuous data. Statistical comparisons between subgroups were evaluated using 2-sample t-tests (or Wilcoxon's rank sum tests) for continuous variables and chi-square tests for categorical variables. All analyses were performed using Stata version 13.

RESULTS

Characteristics of the patients with AS and those with nonradiographic axial SpA. As of July 2015, there were 1,140 patients in the Corrona PsA/SpA Registry with a diagnosis of SpA, excluding patients with PsA. At the time of enrollment, 407 patients met the ASAS criteria for axial SpA, including 310 patients with AS and 97 patients with nonradiographic axial SpA (Figure 1). Among the 97 patients with nonradiographic axial SpA, 29 patients had sacroiliitis on MRI and ≥1 SpA feature, and 81 patients were HLA–B27–positive and had ≥2 other SpA features; 13 patients fulfilled both criteria.

Demographic and defining clinical characteristics. Demographics for all patients with axial SpA, as well as those for the AS and nonradiographic axial SpA subgroups, are shown in Table 1. Overall, in patients with axial SpA, the mean ± SD age was 48.0 ± 13.9 years, the mean ± SD symptom duration was 17.3 ± 12.5 years, 63.6% of the patients were male, and 88.9% of the patients were white. The mean ± SD BMI was 29.5 ± 6.7 kg/m^2 in the overall axial SpA population, with 39.1% of patients considered to be overweight (BMI 25.0 to <30.0 kg/m^2), and 25.9% of patients were considered to be obese (BMI ≥30.0 kg/m^2).
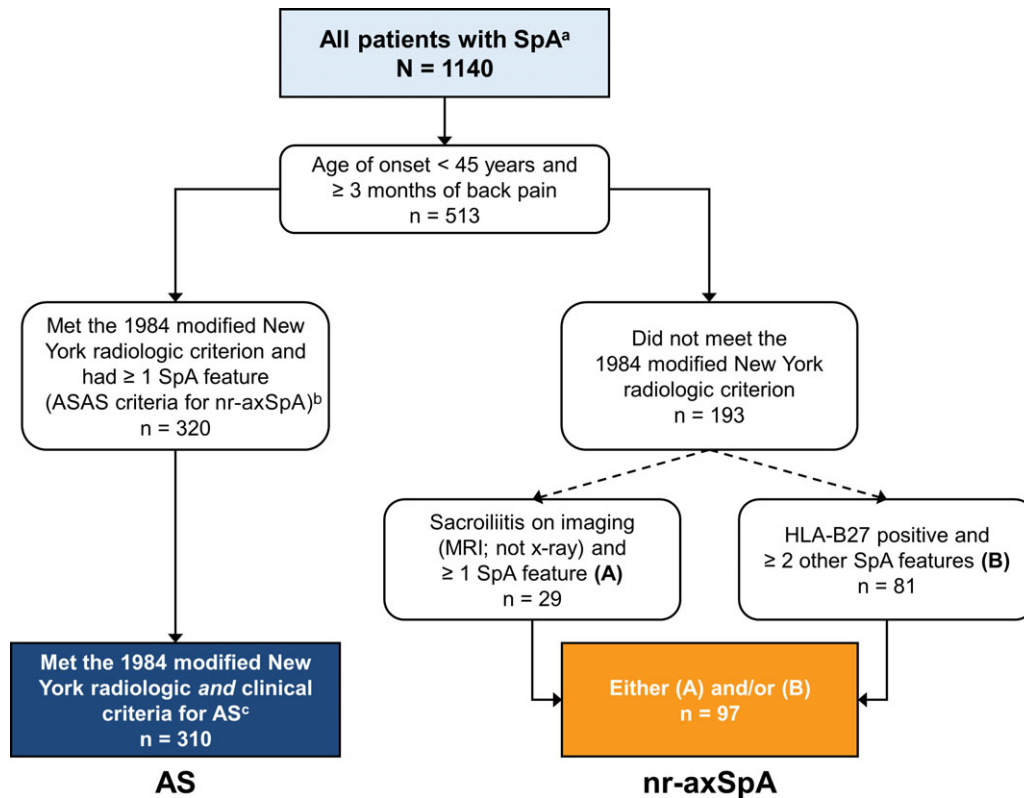
Figure 1. Flow chart of patients with ankylosing spondylitis (AS) and patients with nonradiographic axial spondyloarthritis (nr-axSpA) in the Corrona Psoriatic Arthritis and Spondyloarthritis (PsA/SpA) Registry who were included in the study. ASAS = Assessment of SpondyloArthritis; MRI = magnetic resonance imaging; nr-axSpA = nonradiographic axial spondyloarthritis. a = number includes patients with PsA/SpA. b = the radiologic criterion, defined using the 1984 modified New York criteria for AS, was sacroiliitis grade ≥2 bilaterally or grade ≥3 unilaterally (30). SpA features include inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's/colitis, good response to nonsteroidal antiinflammatory drugs, family history of SpA, HLA–B27 positivity, and elevated C-reactive protein level (5). c = clinical criteria, defined using the 1984 modified New York criteria for AS, included low back pain and stiffness for >3 months that improve with exercise but are not relieved by rest and limitation of motion of the lumbar spine in both the sagittal and frontal planes (30).

At the time of enrollment, BMI, symptom duration, history of comorbidities (cardiovascular disease, cancer, diabetes mellitus, and serious infection), and history of extraarticular manifestations (uveitis, psoriasis, and Crohn's disease/colitis) were similar in the 2 subgroups of patients axial SpA; however, patients with nonradiographic axial SpA were significantly younger (mean ± SD age 43.9 ± 11.6 years and 49.2 ± 14.3 years, respectively; $P < 0.001$) and were more likely to be HLA–B27–positive (82.4% and 66.2%, respectively [$P = 0.02$] according to laboratory records; 85.6% and 64.5%, respectively [$P < 0.001$] according to physician records) compared with patients with AS. The nonradiographic axial SpA subgroup was similar to the AS subgroup in terms of male prevalence (57.3% and 65.6%, respectively; $P = 0.14$), but there was a trend toward a shorter symptom duration in the nonradiographic axial SpA group (mean ± SD 15.0 ± 12.1 years versus 18.0 ± 12.5 years in the AS group; $P = 0.07$).

Approximately two-thirds of all patients (67.1%) in both subgroups had a history of biologic DMARD treatment, and more than one-third of all patients (36.4%) had a history of csDMARD treatment (Table 1). The nonradiographic axial SpA and AS subgroups had a similar prevalence of prior biologic DMARD treatment (74.2% and 64.8%, respectively;

$P = 0.09$) and prednisone treatment (15.5% and 10.3%, respectively; $P = 0.17$), although the percentage of patients with prior use of csDMARDs was significantly higher among those with nonradiographic axial SpA compared with those with AS (45.4% and 33.5%, respectively; $P = 0.04$).

Current medication use was similar between the subgroups patients with axial SpA, suggesting that all patients were being treated similarly, regardless of the presence or absence of radiographic sacroiliitis (Table 1). Overall, 61.9% of patients were receiving a biologic DMARD at baseline (61.3% and 63.9% in the AS and nonradiographic axial SpA groups, respectively). Examination of the type of biologic DMARD used revealed that nearly one-fourth of all patients were receiving a biologic DMARD as monotherapy at baseline, including 23.9% of patients with AS and 24.7% of patients with nonradiographic axial SpA. Another one-fourth of all patients were receiving a biologic DMARD plus an NSAID at baseline (25.2% and 24.7% of patients with AS and patients with nonradiographic axial SpA, respectively). Approximately 13% of all patients were receiving a biologic DMARD in combination with a csDMARD; 5.7% of all patients also received an NSAID, and 7.1% did not. At baseline, >50% of all patients (51.8%) in the study

Table 1. Baseline demographic and defining clinical characteristics of the patients*

Characteristic	Overall (n = 407)	AS (n = 310)	Nonradiographic axial SpA (n = 97)	P
Age, mean ± SD years	48.0 ± 13.9	49.2 ± 14.3	43.9 ± 11.6	0.001
Male	255 (63.6)	200 (65.6)	55 (57.3)	0.14
Race				0.13
White	362 (88.9)	279 (90.0)	83 (85.6)	–
Asian	11 (2.8)	6 (2.0)	5 (5.3)	–
Black	6 (1.5)	5 (1.7)	1 (1.1)	–
Pacific Islander	3 (0.8)	1 (0.3)	2 (2.1)	–
Mixed race	7 (1.8)	4 (1.3)	3 (3.2)	–
Other	3 (0.8)	3 (1.0)	0 (0.0)	–
BMI, mean ± SD kg/m^2	29.5 ± 6.7	29.6 ± 6.7	29.3 ± 6.5	0.72
BMI classification				0.92
Normal/underweight (<25.0 kg/m^2)	135 (35.0)	102 (34.6)	33 (36.3)	–
Overweight (25.0 to <30.0 kg/m^2)	151 (39.1)	117 (39.7)	34 (37.4)	–
Obese (≥30.0 kg/m^2)	100 (25.9)	76 (25.8)	24 (26.4)	–
Symptom duration, mean ± SD years	17.3 ± 12.5	18.0 ± 12.5	15.0 ± 12.1	0.07
Disease duration, mean ± SD years	10.4 ± 11.3	11.1 ± 12.0	8.0 ± 8.5	0.02
HLA–B27				
Patients with available HLA–B27 test results (reported on laboratory form)	222 (54.5)	154 (50.0)	68 (70.1)	0.008
Positive test result (among patients with available test results)	158 (71.2)	102 (66.2)	56 (82.4)	0.02
HLA–B27 positivity (physician reported)	283 (69.5)	200 (64.5)	82 (85.6)	<0.001
Family history of SpA	58 (14.2)	37 (11.9)	21 (21.6)	0.02
History of comorbidities				
Hypertension and/or hyperlipidemia	152 (37.3)	34 (35.0)	118 (38.1)	0.59
Cardiovascular disease†	39 (9.6)	30 (9.7)	9 (9.2)	0.91
Diabetes mellitus	29 (7.1)	23 (7.4)	6 (6.2)	0.68
Any cancer‡	21 (5.2)	16 (5.2)	5 (5.2)	1.00
Fibromyalgia	17 (4.2)	12 (3.9)	5 (5.2)	0.58
Serious infection§	0	0	0	
History of extraarticular manifestations				
Uveitis	70 (17.2)	52 (16.8)	18 (18.6)	0.69
Psoriasis	42 (10.3)	31 (10.0)	11 (11.3)	0.71
Crohn's disease or colitis	29 (7.1)	23 (7.4)	6 (6.2)	0.68
Prior medication use				
bDMARD¶	273 (67.1)	201 (64.8)	72 (74.2)	0.09
csDMARD#	148 (36.4)	104 (33.5)	44 (45.4)	0.04
Prednisone	47 (11.5)	32 (10.3)	15 (15.5)	0.17
Current medication use				0.65
NSAID only	69 (17.0)	56 (18.1)	13 (13.4)	–
csDMARD only	19 (4.7)	12 (3.9)	7 (7.2)	–
csDMARD + NSAID	17 (4.2)	12 (3.9)	5 (5.2)	–
bDMARD only	98 (24.1)	74 (23.9)	24 (24.7)	–
bDMARD + NSAID	102 (25.1)	78 (25.2)	24 (24.7)	–
bDMARD + csDMARD	29 (7.1)	23 (7.4)	6 (6.2)	–
bDMARD + csDMARD + NSAID	23 (5.7)	15 (2.8)	8 (8.3)	–
None	50 (12.3)	40 (12.9)	10 (10.3)	–

* All values were calculated based on available data. For all variables, <20% of data were missing, except for symptom duration (available for 317 patients). Except where indicated otherwise, values are the number (%). AS = ankylosing spondylitis; SpA = spondyloarthritis; BMI = body mass index; bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic DMARD; NSAID = nonsteroidal antiinflammatory drug; SpA = spondyloarthritis.

† Combined history of myocardial infarction, acute coronary syndrome, coronary artery disease, congestive heart failure, peripheral artery disease, cardiac revascularization procedure, ventricular arrhythmia, cardiac arrest, unstable angina, stroke, transient ischemic attack, pulmonary embolism, carotid artery disease, deep vein thrombosis, or other cardiovascular event.

‡ Excluding non-melanoma skin cancer.

§ Includes infections that led to hospitalization or intravenous antibiotics, including joint/bursa, cellulitis, sinusitis, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis, urinary tract infection, upper respiratory tract infection, or infection of another specified site.

¶ Prior/current biologic DMARDs may include abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and/or ustekinumab.

Prior/current csDMARDs may include hydroxychloroquine, leflunomide, methotrexate, and/or sulfasalazine.

were receiving NSAIDs, which are recommended as first-line treatment in the 2015 ACR/SAA/SPARTAN guidelines for the treatment of AS and nonradiographic axial SpA (23) and the 2016 ASAS-EULAR management recommendations for axial SpA (24), while 21.6% of patients were receiving csDMARDs at baseline.

Baseline clinical features and disease measures. A significantly higher proportion of patients with nonradiographic axial SpA had current enthesitis (47.4% and 29.0%, respectively; $P < 0.001$) and had a higher mean $\pm$ SD SPARCC Enthesitis Index score (4.9 $\pm$ 3.3 and 3.1 $\pm$ 2.4, respectively; $P = 0.002$) compared with patients with AS (Table 2). Although the percentage of patients with dactylitis was slightly, but not significantly, higher among those with nonradiographic axial SpA compared with patients with AS (12.4% and 9.0%, respectively; $P = 0.34$), patients with AS had significantly higher mean $\pm$ SD dactylitis counts (4.7 $\pm$ 3.8 and 1.0 $\pm$ 0.0, respectively; $P < 0.001$). Patients with AS also had significantly higher mean $\pm$ SD tender joint counts (5.6 $\pm$ 10.3 and 2.7 $\pm$ 6.7, respectively; $P = 0.001$), although mean $\pm$ SD swollen joint counts were similar between the nonradiographic axial SpA and AS groups (1.0 $\pm$ 2.8 and 1.0 $\pm$ 3.8, respectively; $P = 0.31$).

Overall, patients with axial SpA had active disease (mean $\pm$ SD BASDAI 4.3 $\pm$ 2.5; mean $\pm$ SD ASDAS 2.1 $\pm$ 0.8) and functional disability (mean $\pm$ SD BASFI 3.5 $\pm$ 2.8), with no notable differences between the AS and nonradiographic axial SpA subgroups. Patients with nonradiographic axial SpA appeared to have less-impaired spinal mobility than patients with AS, as demonstrated by a significantly lower mean $\pm$ SD occiput-to-wall distance (3.1 $\pm$ 6.1 cm and 4.9 $\pm$ 7.0 cm, respectively; $P = 0.03$) and

significantly increased lateral lumbar flexion (26.3 $\pm$ 19.3 cm and 20.7 $\pm$ 0.8 cm, respectively; $P = 0.01$). Patients with nonradiographic axial SpA had a significantly lower ESR (8.9 $\pm$ 8.6 mm/hour versus 14.4 $\pm$ 18.8 mm/hour; $P = 0.02$) and a slightly lower, although not statistically significant, mean $\pm$ SD CRP level (1.9 $\pm$ 4.3 mg/liter and 2.7 $\pm$ 7.6 mg/liter, respectively; $P = 0.44$) compared with patients with AS.

Baseline patient-reported outcomes. Patients with AS and those with nonradiographic axial SpA were both impacted by their disease, as assessed by multiple patient-reported outcome measures (Table 3). Overall, all patients reported pain, fatigue, morning stiffness, and functional disability as measured by the HAQ-S, with no significant differences between the AS and nonradiographic axial SpA groups. In addition, patients in both groups missed an average 6.3% of work time due to a disease-related problem and experienced a $\geq$25% reduction in work productivity and activity. However, the mean percentages of patients with presenteeism (i.e., impairment at work or and/or reduced on-the-job effectiveness) and overall activity impairment were significantly greater among those with nonradiographic axial SpA compared with those with AS (32.6% and 24.2%, respectively [$P = 0.02$] and 36.6% and 28.6%, respectively [$P = 0.04$]).

DISCUSSION

This study of patients from the Corrona PsA/SpA Registry represents one of the first national-level analyses of patients with nonradiographic axial SpA and patients with AS from multiple geographic regions and a mix of primary and tertiary clinical centers across the US. Although the criteria for classification of nonradiographic axial SpA were

Table 2. Baseline clinical features and measures of disease activity, physical function, and spinal mobility*

Characteristic	Overall group (n = 407)	AS (n = 310)	Nonradiographic axial SpA (n = 97)	P
Enthesitis, no. (%)	136 (33.4)	90 (29.0)	46 (47.4)	<0.001
SPARCC Enthesitis Index score in patients with enthesitis, mean $\pm$ SD (1–16 scale)	3.7 $\pm$ 2.9	3.1 $\pm$ 2.4	4.9 $\pm$ 3.3	0.002
Dactylitis, no. (%)	40 (9.8)	28 (9.0)	12 (12.4)	0.34
Dactylitis count in patients with dactylitis, mean $\pm$ SD (range 1–20)	4.4 $\pm$ 3.7	4.7 $\pm$ 3.8	1.0 $\pm$ 0.0	<0.001
History of dactylitis, no. (%)	18 (4.4)	9 (2.9)	9 (9.3)	0.008
No. of tender joints (68 assessed), mean $\pm$ SD	3.4 $\pm$ 7.8	2.7 $\pm$ 6.7	5.6 $\pm$ 10.3	0.001
No. of swollen joints (66 assessed), mean $\pm$ SD	1.0 $\pm$ 3.6	1.0 $\pm$ 3.8	1.0 $\pm$ 2.8	0.31
Swollen joint count $\geq$1, no. (%)	81 (20.3)	58 (19.2)	23 (23.7)	0.34
BASDI score, mean $\pm$ SD (range 0–10)	4.3 $\pm$ 2.5	4.2 $\pm$ 2.4	4.6 $\pm$ 2.6	0.16
BASFI score, mean $\pm$ SD (range 0–10)	3.5 $\pm$ 2.8	3.6 $\pm$ 2.8	3.3 $\pm$ 2.7	0.34
Spinal mobility measures				
Occiput-to-wall distance, mean $\pm$ SD cm	4.5 $\pm$ 6.9	4.9 $\pm$ 7.0	3.1 $\pm$ 6.1	0.03
Lateral lumbar flexion (average of right and left), mean $\pm$ SD cm	22.0 $\pm$ 18.8	20.7 $\pm$ 0.8	26.3 $\pm$ 19.3	0.01
ASDAS, mean $\pm$ SD	2.1 $\pm$ 0.8	2.0 $\pm$ 0.8	2.2 $\pm$ 0.8	0.65
CRP, mean $\pm$ SD mg/liter	2.5 $\pm$ 7.0	2.7 $\pm$ 7.6	1.9 $\pm$ 4.3	0.44
Elevated CPR level, no. (%)	83 (20.4)	64 (20.7)	19 (19.6)	0.82
ESR, mean $\pm$ SD mm/hour	13.0 $\pm$ 16.8	14.4 $\pm$ 18.8	8.9 $\pm$ 8.6	0.02
History of psoriasis, no. (%)	31 (7.6)	20 (6.5)	11 (11.3)	0.11

* All values were calculated based on available data. For all variables, <20% of data were missing, except for the Ankylosing Spondylitis Disease Activity Score (ASDAS) (available for 74 patients), C-reactive protein (CRP) (available for 257 patients), and erythrocyte sedimentation rate (ESR) (available for 246 patients). AS = ankylosing spondylitis; SpA = spondyloarthritis; SPARCC = Spondyloarthritis Research Consortium of Canada; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index.

Table 3. Baseline patient-reported outcome measures*				
Characteristic	**Overall (n = 407)**	**AS (n = 310)**	**Nonradiographic axial SpA (n = 97)**	***P***
Patient-reported pain, mean ± SD†	44.6 ± 29.8	43.9 ± 29.8	46.8 ± 29.7	0.44
Patient-reported fatigue, mean ± SD†	48.3 ± 29.2	47.8 ± 29.4	50.2 ± 28.7	0.48
Morning stiffness				0.95
Yes	368 (90.4)	277 (89.3)	91 (93.8)	
<30 minutes	88 (23.9)	66 (23.8)	22 (24.2)	
≥30 minutes	280 (76.1)	211 (76.2)	69 (75.8)	
HAQ-S, mean ± SD (range 0–3)	0.7 ± 0.6	0.7 ± 0.6	0.7 ± 0.6	0.63
EQ-5D, mean ± SD (range 0–1)	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.98
WPAI				
Absenteeism (work time missed)	6.3 (17.7)	6.1 (16.8)	7.0 (20.0)	0.73
Presenteeism (impairment at work/reduced on-the-job effectiveness)	26.5 (26.1)	24.2 (23.8)	32.6 (30.8)	0.02
Work productivity loss (overall work impairment/absenteeism plus presenteeism)	28.1 (27.2)	26.8 (25.8)	31.6 (30.8)	0.23
Activity impairment	30.7 (28.7)	28.6 (27.4)	36.6 (31.6)	0.04
Currently employed	273 (68.6)	199 (65.5)	74 (78.7)	0.02

* All values were calculated based on available data. Except where indicated otherwise, values are the number (%). AS = ankylosing spondylitis; SpA = spondyloarthropathy; HAQ-S = Health Assessment Questionnaire for Spondyloarthropathies; EQ-5D = EuroQol 5-domain questionnaire; WPAI = Work Productivity and Activity Impairment questionnaire.
† Scored on a 0–100-mm visual analog scale.

established in 2009 (5), patients with nonradiographic axial SpA have been described in only a limited number of clinical trials, registry reports, and observational studies, most of which were conducted outside of the US (8–18,26–29, 31–33). In clinical trial settings, patients with nonradiographic axial SpA were typically defined as those who met the ASAS classification criteria for axial SpA but did not meet the radiology criterion of the 1984 modified New York criteria for AS, similar to the definition used in the current analysis (26–29).

Our findings were consistent with those of previously published clinical trials and observational studies from outside of the US, which showed that despite some differences in patient and clinical characteristics, patients with nonradiographic axial SpA and those with AS were mostly similar and shared significant disease burden (9–18,26–29,31–33). In the current study, patients with nonradiographic axial SpA were younger, more often had enthesitis, and had better spinal mobility; however, the percentages of patients with presenteeism and overall activity impairment were significantly greater among those with nonradiographic axial SpA compared with those with AS. There were no differences between these groups in prior/current biologic DMARD treatment, disease activity and function (BASDAI, BASFI, ASDAS, and HAQ-S), quality of life, pain, fatigue, or absenteeism and work productivity loss.

The difference between AS and nonradiographic axial SpA in presenteeism and activity impairment is an interesting finding, because there have been limited studies of work productivity and activity impairment according to radiographic status. In a primary care cohort of patients with chronic low back pain in The Netherlands, patients with AS reported increased absenteeism, presenteeism, and work productivity compared with those with nonradiographic axial SpA (34); however, the sample sizes

were small (14 patients with AS and 48 patients with nonradiographic axial SpA), and no significant differences were observed. Further research is needed to better understand the relative burden of nonradiographic axial SpA and AS in the workplace. We also acknowledge that csDMARDs are not recommended for treatment of patients with axial SpA, and in our study we observed csDMARD use in ~22% of patients; however, surveys of rheumatology practices in multiple geographic regions have shown that despite the lack of evidence of efficacy of csDMARDs, use of these agents to treat the spectrum of axial SpA is not infrequent. This observation is consistent with findings from the Management of Axial SpA International and Multicentric Approaches survey, which demonstrated that ~70–80% of both academic and community rheumatologists used methotrexate, with even higher proportions prescribing sulfasalazine, for the management of patients with axial SpA (35).

Other studies have demonstrated the substantial disease burden in patients with nonradiographic axial SpA, but only a few studies have specifically examined whether these patients and patients with AS benefit from the same treatments. Two clinical trials included AS and nonradiographic axial SpA populations and directly compared the response to treatment with certolizumab pegol (RAPID-axSpA) or etanercept (ESTHER) over time (27,31). All patients in the RAPID-axSpA study were required to have objective signs of active inflammation (e.g., elevated CRP level or active inflammation on MRI); at baseline, the AS subgroup had a higher proportion of males, while the nonradiographic axial SpA subgroup was younger with a shorter disease duration and lower CRP levels (27). In the ESTHER trial, patients with AS and those with nonradiographic axial SpA were mostly similar, except patients with nonradiographic axial SpA

had higher mean ± SD CRP levels compared with patients with AS (13.3 ± 5.7 mg/liter and 9.4 ± 9.9 mg/liter, respectively); however, the sample sizes were small, with only 20 patients per cohort (31). Notably, neither study showed a significant difference in the treatment response between patients with AS and patients with nonradiographic axial SpA (27,31), suggesting that patients with nonradiographic axial SpA do not respond to treatment differently from those with AS and should benefit equally from the same treatments.

The use of TNF inhibitors for the treatment of nonradiographic axial SpA has also been explored in clinical practice outside of the US. Data from the Swiss Clinical Quality Management Cohort showed that nearly two-thirds of patients who fulfilled the ASAS classification criteria for axial SpA, regardless of radiographic status, initiated TNF inhibitor therapy after inclusion, suggesting that the indications for TNF inhibitor treatment were similar in patients with and those without radiographic involvement (16). Among 708 patients with early inflammatory back pain suggestive of axial SpA in the French DESIR cohort, 23.4% and 30.2% of patients received a TNF inhibitor within 12 and 24 months of follow-up, respectively (36,37).

In the current study, we observed no significant differences between groups in the proportions of patients with prior biologic DMARD treatment (74.2% and 64.8% in nonradiographic axial SpA and AS, respectively) or current biologic DMARD treatment (63.9% and 61.3% in nonradiographic axial SpA and AS, respectively). These findings indicate that physicians may already be treating all patients with axial SpA similarly in US clinical practice, irrespective of the presence of radiographic sacroiliitis. This is remarkable, because biologic DMARDs are not licensed for the treatment of nonradiographic axial SpA in the US. Further research is needed to address the knowledge gap regarding whether any similarities or differences between patients with nonradiographic axial SpA and patients with AS should influence management and treatment.

As in any observational study, patients in the current study, who are routinely seen and treated by rheumatologists voluntarily participating in the Corrona registry, may not be representative of all adults with axial SpA in the US, many of whom are not being treated by a rheumatologist. Because laboratory tests are not mandated by the Corrona protocol, a reduced number of patients had available data for the ESR, CRP, or ASDAS; this may reflect practice patterns of treating physicians in the US. The proportion of patients in the predominantly white AS group with HLA–B27 positivity based on either laboratory records (66.2%) or physician reports (64.5%) was relatively low compared with typical estimates of 85–95% of white patients with AS (38), potentially bringing into question the reliability of the diagnosis by rheumatologists. Although the physician reports may have underestimated HLA–B27 positivity, because an empty checkbox on the form was assumed to represent HLA–B27 negativity, the rate was consistent with the laboratory values. However, HLA–B27 positivity is not mandatory for a diagnosis of AS, and patients in the current study were selected based on fulfillment of specific radiologic and clinical criteria in addition to a diagnosis by the rheumatologist.

Obtaining an HLA–B27 test result was not mandatory in the Corrona Registry; therefore, the low percentage with HLA–B27 positivity does not indicate that these patients never had an HLA–B27 test in their lifetimes, but that it might not have been captured in the registry. Because this was a descriptive, cross-sectional study of patients at the time of enrollment, no longitudinal analyses were performed to directly compare and contrast patients with AS and those with nonradiographic axial SpA over time.

This study provides a descriptive characterization of a large cohort of patients with AS and patients with nonradiographic axial SpA enrolled in a single US registry. Our findings align with those of previous studies, most of which were conducted outside of the US. Although there were some differences between patients with nonradiographic axial SpA and those with AS, both groups shared a high level of disease burden, with similar measures of disease activity, disease function, and patient-reported outcomes. Taken together, our results support the hypothesis that nonradiographic axial SpA and AS represent 2 aspects of the same disease presentation, that this distinction may not be clinically relevant, and that patients with nonradiographic axial SpA and patients with AS should be treated similarly (24,25,39–42). Additional studies are needed to better understand the clinical manifestations and progression of nonradiographic axial SpA and AS to further examine what implications, if any, this differentiation has on management of axial SpA.

AUTHOR CONTRIBUTIONS

REFERENCES

1. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017; 390:73–84.
2. Reveille JD. Epidemiology of spondyloarthritis in North America. Am J Med Sci 2011;341:284–6.

3. Reveille JD, Witter JP, Weisman MH. Prevalence of axial spondyloarthritis in the United States: estimates from a cross-sectional survey. Arthritis Care Res (Hoboken) 2012;64:905–10.

4. Reveille JD, Weisman MH. The epidemiology of back pain, axial spondyloarthritis and HLA-B27 in the United States. Am J Med Sci 2013;345:431–6.

5. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, 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;68:777–83.

6. Boonen A, Sieper J, van der Heijde D, Dougados M, Bukowski JF, Valluri S, et al. The burden of non-radiographic axial spondyloarthritis. Semin Arthritis Rheum 2015;44:556–62.

7. 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;34:975–83.

8. Deodhar A, Mease PJ, Reveille JD, Curtis JR, Chen S, Malhotra K, et al. Frequency of axial spondyloarthritis diagnosis among patients seen by US rheumatologists for evaluation of chronic back pain. Arthritis Rheumatol 2016;68:1669–76.

9. Jeong H, Yoon JY, Park EJ, Hwang J, Kim H, Ahn JK, et al. Clinical characteristics of nonradiographic axial spondyloarthritis in Korea: a comparison with ankylosing spondylitis. Int J Rheum Dis 2015;18:661–8.

10. Kiltz U, Baraliakos X, Karakostas P, Igelmann M, Kalthoff L, Klink C, et al. Do patients with non-radiographic axial spondyloarthritis differ from patients with ankylosing spondylitis? Arthritis Care Res (Hoboken) 2012;64:1415–22.

11. 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;18:736–41.

12. Poddubnyy DA, Rudwaleit M, Listing J, Braun J, Sieper J. Comparison of a high sensitivity and standard C reactive protein measurement in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis. Ann Rheum Dis 2010;69:1338–41.

13. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Marker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum 2009;60:717–27.

14. Wallman JK, Kapetanovic MC, Petersson IF, Geborek P, Kristensen LE. Comparison of non-radiographic axial spondyloarthritis and ankylosing spondylitis patients: baseline characteristics, treatment adherence, and development of clinical variables during three years of anti-TNF therapy in clinical practice. Arthritis Res Ther 2015;17:378.

15. Blachier M, Canoui-Poitrine F, Dougados M, Lethuaut A, Fautrel B, Ferkal S, et al. Factors associated with radiographic lesions in early axial spondyloarthritis: results from the DESIR cohort. Rheumatology (Oxford) 2013;52:1686–93.

16. Ciurea A, Scherer A, Exer P, Bernhard J, Dudler J, Beyeler B, et al. Tumor necrosis factor α inhibition in radiographic and nonradiographic axial spondyloarthritis: results from a large observational cohort. Arthritis Rheum 2013;65:3096–106.

17. Van den Berg R, de Hooge M, van Gaalen F, Reijnierse M, Huizinga T, van der Heijde D. Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. Rheumatology (Oxford) 2013;52:1492–9.

18. Wallis D, Haroon N, Ayearst R, Carty A, Inman RD. Ankylosing spondylitis and nonradiographic axial spondyloarthritis: part of a common spectrum or distinct diseases? J Rheumatol 2013;40:2038–41.

19. Poddubnyy D, Haibel H, Listing J, Marker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum 2012;64:1388–98.

20. Poddubnyy D, Protopopov M, Haibel H, Braun J, Rudwaleit M, Sieper J. High disease activity according to the Ankylosing Spondylitis Disease Activity Score is associated with accelerated radiographic spinal progression in patients with early axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort. Ann Rheum Dis 2016;75:2114–8.

21. Ramiro S, van der Heijde D, van Tubergen A, Stolwijk C, Dougados M, van den Bosch F, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. Ann Rheum Dis 2014;73:1455–61.

22. Dougados M, Demattei C, van den Berg R, Vo Hoang V, Thevenin F, Reijnierse M, et al. Rate and predisposing factors for sacroiliac joint radiographic progression after a two-year follow-up period in recent-onset spondyloarthritis. Arthritis Rheumatol 2016;68:1904–13.

23. Ward MM, Deodhar A, Akl EA, Lui A, Ermann J, Gensler LS, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol 2016;68:282–98.

24. Van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978–91.

25. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011;70:896–904.

26. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis 2013;72:815–22.

27. Landewé R, Braun J, Deodhar A, Dougados M, Maksymowych WP, Mease PJ, 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;73:39–47.

28. Dougados M, van der Heijde D, Sieper J, Braun J, Maksymowych WP, Citera G, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol 2014;66:2091–102.

29. Sieper J, van der Heijde D, Dougados M, Maksymowych WP, Scott BB, Boice JA, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2015;67:2702–12.

30. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.

31. Song IH, Weiss A, Hermann KG, Haibel H, Althoff CE, Poddubnyy D, 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;72:823–5.

32. Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis Rheum 2008;58:1981–91.

33. Song IH, Hermann K, Haibel H, Althoff CE, Listing J, Burmester G, et al. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. Ann Rheum Dis 2011;70:590–6.

34. Van Hoeven L, Boonen A, Hazes JM, Weel AE. Work outcome in yet undiagnosed patients with non-radiographic

axial spondyloarthritis and ankylosing spondylitis: results of a cross-sectional study among patients with chronic low back pain. Arthritis Res Ther 2017;19:143.

35. Van der Heijde D, Sieper J, Elewaut D, Deodhar A, Pangan AL, Dorr AP. Referral patterns, diagnosis, and disease management of patients with axial spondyloarthritis: results of an international survey. J Clin Rheumatol 2014;20:411–7.

36. Canoui-Poitrine F, Poulain C, Molto A, Le Thuaut A, Lafon C, Ferrenq V, et al. Early tumor necrosis factor α antagonist therapy in everyday practice for inflammatory back pain suggesting axial spondyloarthritis: results from a prospective multicenter French cohort. Arthritis Care Res (Hoboken) 2014;66:1395–402.

37. Moltó A, Patemotte S, Claudepierre P, Breban M, Dougados M. Effectiveness of tumor necrosis factor α blockers in early axial spondyloarthritis: data from the DESIR cohort. Arthritis Rheumatol 2014;66:1734–44.

38. Reveille JD. Biomarkers for diagnosis, monitoring of progression, and treatment responses in ankylosing spondylitis and axial spondyloarthritis. Clin Rheumatol 2015;34:1009–18.

39. Baraliakos X, Braun J. Non-radiographic axial spondyloarthritis and ankylosing spondylitis: what are the similarities and differences? RMD Open 2015;1 Suppl 1:e000053.

40. Braun J, Baraliakos X, Kiltz U. Non-radiographic axial spondyloarthritis: a classification or a diagnosis? Clin Exp Rheumatol 2016;34:1 Suppl 95:S5–6.

41. Poddubnyy D, Sieper J. Similarities and differences between nonradiographic and radiographic axial spondyloarthritis: a clinical, epidemiological and therapeutic assessment. Curr Opin Rheumatol 2014;26:377–83.

42. 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;75:791–4.