Original article

Characteristics of patients with axial spondyloarthritis by geographic regions: PROOF multicountry observational study baseline results

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Abstract

Objectives. To compare demographic and clinical characteristics of patients with axial SpA (axSpA) across geographic regions.

Methods. Patients With Axial Spondyloarthritis: Multicountry Registry of Clinical Characteristics (PROOF) is an observational study that enrolled recently diagnosed ($\leq$1 year) axSpA patients fulfilling the Assessment of SpondyloArthritis international Society classification criteria from rheumatology clinical practices in 29 countries across six geographic regions. Demographics and disease-related parameters were collected. Here we present baseline data for patients who were classified as radiographic axSpA (r-axSpA) or non-radiographic axSpA (nr-axSpA) confirmed by central reading.

Results. Of the 2170 patients enrolled, 1553 were classified based on central evaluation of sacroiliac radiographs [r-axSpA: 1023 (66%); nr-axSpA: 530 (34%)]. Patients with nr-axSpA had a significantly higher occurrence of enthesitis (40% *vs* 33%), psoriasis (10% *vs* 5%) and IBD (4% *vs* 2%) *vs* r-axSpA patients. Significant differences in axSpA characteristics were observed between geographic regions. The highest occurrence of peripheral arthritis (60%), enthesitis (52%) and dactylitis (12%) was in Latin America, and the lowest was in Canada (9%, 9% and 2%, respectively). The occurrence of uveitis and psoriasis was highest in Canada (18% and 14%, respectively) and lowest in China (6% and <1%, respectively). IBD was highest in Arabia (21%), and no cases were observed in China. In multivariable analysis adjusted for factors potentially affecting peripheral and extramusculoskeletal manifestations, geographic regions still exhibited significant differences in frequencies of uveitis ($P < 0.01$), psoriasis ($P < 0.0001$) and peripheral arthritis ($P < 0.0001$).

Conclusion. The multinational PROOF study of axSpA patients showed significant regional differences in peripheral and extramusculoskeletal manifestations of SpA, which could be considered in management guidelines and clinical trials.

Key words: axial spondyloarthritis, radiographic, non-radiographic, characteristics, demographics

CLINICAL SCIENCE

Rheumatology key messages

- PROOF enrolled patients with recently diagnosed axial spondyloarthritis in 29 countries in six geographic regions.
- Demographic characteristics, peripheral and extramusculoskeletal manifestations, disease activity and treatment differed by geographic region.
- Regional differences in clinical characteristics should be considered in management recommendations and clinical trial planning.

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Introduction

Axial SpA (axSpA), which encompasses radiographic axSpA (r-axSpA, also known as AS) and non-radiographic axSpA (nr-axSpA), is an immune-mediated inflammatory disease primarily affecting the axial skeleton [1, 2]. The symptoms of axSpA usually start between 20 and 30 years of age, and historically there has been a considerable delay between symptom onset and diagnosis (5–11 years) [3–5]. The prevalence of axSpA is estimated to range from 0.3 to 1.4% worldwide [2, 6]. The most frequent axSpA symptom is chronic, often inflammatory back pain that might be difficult to distinguish from other causes of chronic back pain (CBP) [1, 2]. Other musculoskeletal manifestations of axSpA include peripheral arthritis, enthesitis and, less frequently, dactylitis [1, 2, 7–9]. AxSpA may also present with extramusculoskeletal manifestations (EMMs), such as psoriasis, uveitis and IBD [10].

The classification of axSpA patients into r-axSpA and nr-axSpA is based on the presence or absence of radiographic sacroiliitis (according to the radiographic criterion of the modified New York criteria for AS) [11] on plain pelvic radiographs [12]. In studies of patients with newly diagnosed axSpA, 23–80% were classified as having nr-axSpA, which is substantially dependent on the disease duration at the time of diagnosis [13].

Patients With Axial Spondyloarthritis: Multicountry Registry of Clinical Characteristics (PROOF), including radiographic progression and burden of disease over 5 years in real-life settings, is a large, multicountry, prospective, observational study in recently diagnosed axSpA patients in rheumatology clinical practice. This analysis presents the baseline demographic and clinical characteristics of patients involved in the PROOF study, with emphasis on the clinical presentations across geographic regions.

Methods

Study design

PROOF is an ongoing study conducted in rheumatology clinical practices in 29 countries across six geographic regions worldwide (Supplementary Fig. S1, available at *Rheumatology* online). The study was approved by local ethics committees of each study site in accordance with local laws and regulations (Supplementary Table S1, available at *Rheumatology* online) and is being conducted in accordance with the Declaration of Helsinki. Adult patients diagnosed with axSpA ≤1 year before study enrolment and fulfilling the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA were considered eligible. Prior to inclusion, patients provided written informed consent where applicable and written authorization to use and/or disclose anonymized health data and to send anonymized imaging of SI joints to a central reading centre.

Assessments

At baseline (visit 1 in the study), the demographic and clinical data related to the diagnosis and treatment of axSpA, disease activity, quality of life (QoL), work productivity and pelvic anteroposterior conventional radiographs were collected. Investigator confidence with the diagnosis of axSpA was ascertained on a numeric rating scale (0–10; 0 = not confident at all and 10 = very confident) at enrolment. The presence (past or present) of inflammatory back pain, peripheral manifestations (peripheral arthritis, enthesitis and dactylitis) and EMMs (anterior uveitis, IBD and psoriasis) was recorded. Disease activity was evaluated using the BASDAI, Patient Global Assessment (PtGA) and AS Disease Activity Score with CRP (ASDAS-CRP). Physical function was measured by the BASFI.

Health-related QoL (HRQoL) was measured using the 12-item Short Form Health Survey version 2 (SF-12v2). Activity impairment was evaluated by the Work Productivity and Activity Impairment–Specific Health Problem (WPAI-SHP) questionnaire. Past and current treatments for axSpA were recorded. MRI of the SI joints was also conducted in some patients.

Classification of patient disease as r-axSpA or nr-axSpA

The classification as either r- or nr-axSpA was based on the grading of sacroiliitis on the anteroposterior pelvic radiographs; grading was in accordance with the modified New York criteria for AS [11] (grade 0–4 for each SI joint). Patients with sacroiliitis of grade ≥2 bilaterally or grade ≥3 unilaterally were classified as having r-axSpA; otherwise they were classified as having nr-axSpA. The radiographs were assessed first by a local reader, followed by a central reader. In case of a disagreement in the classification (r- or nr-axSpA) between the local and central reader, the radiograph was evaluated by a second central reader (adjudicator) who was blinded to the previous assessments, and this assessment determined the final classification.

Statistical analysis

Baseline data for patients with available radiographs in whom the classification of r- or nr-axSpA was verified by central reading (referred to here as the total axSpA population) are reported here. The descriptive statistics of baseline demographics and clinical characteristics were compared between patients with r- and nr-axSpA in the total axSpA population using a two-sided *t*-test for continuous variables and Fisher's exact test for categorical variables. The patients in the total axSpA population were then divided into six geographic regions: Europe, China, Latin America, Canada, Arab countries (Arabia) and South Africa [however, due to the small number of patients in South Africa (*n* = 14), only limited findings are presented]. The grouping of countries in the six geographic regions is depicted in Supplementary Fig. S1, available at *Rheumatology* online. The baseline

demographics and clinical characteristics were compared across the regions using analysis of variance for continuous variables or the chi-squared test for categorical variables for the total axSpA population and separately for r-axSpA and nr-axSpA subpopulations. Analysis of covariance was used to adjust the interregion differences in the frequencies of peripheral and EMMs for age, sex, time from onset of CBP to diagnosis or visit 1, HLA-B27 positivity, BASDAI, CRP and use of conventional synthetic DMARDs (csDMARDs) and TNF inhibitors. The statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC, USA).

Patient and public involvement

This research was done without any formal patient/patient organization involvement in the study design, development of patient-relevant outcomes, interpretation of results or the writing or editing of the manuscript.

Results

Demographic and clinical characteristics of the total axSpA population

A total of 2170 patients with axSpA fulfilled the ASAS classification criteria and were enrolled between 27 January 2014 and 30 August 2015 (Fig. 1). Based on the central reading of pelvic radiographs, a total of 1553 patients were classified as r-axSpA [1023 (66%)] and nr-axSpA [530 (34%)] and were included in the current analysis. The remaining 617 patients were excluded from this analysis because pelvic radiographs were not provided to the central reading centre and therefore no standardized classification was possible; the characteristics of these patients were similar to the overall population (Supplementary Table S2, available at *Rheumatology* online).

The mean level of confidence with the diagnosis of axSpA by the investigators was 8.7 (S.D. 1.8). Of the 1553 patients classified based on central reading, 975 were classified as r-axSpA and 568 as nr-axSpA by

local readers (local reader data were missing for 7 patients who were classified as r-axSpA and 3 patients classified as nr-axSpA per central reading); 17% of these patients were reclassified after the central reading, while 83% retained the initial classification.

Significantly more r-axSpA *vs* nr-axSpA patients were men (71% *vs* 48%), were HLA-B27 positive (69% *vs* 56%) and had elevated CRP (53% *vs* 32%; Table 1). In contrast, nr-axSpA patients had significantly higher frequencies of current/past enthesitis (40% *vs* 33%), psoriasis (10% *vs* 5%) and IBD (4% *vs* 2%) and shorter symptom duration (48 months *vs* 61 months) compared with r-axSpA patients. The presence of active sacroiliitis on MRI was recorded for 298 patients with r-axSpA and 282 patients with nr-axSpA by the local investigator at baseline (Table 1).

Significantly higher proportions of patients with r-axSpA were treated with TNF inhibitors compared with nr-axSpA patients (17% *vs* 11%). csDMARDs other than SSZ and MTX were also more frequently used in r-axSpA *vs* nr-axSpA patients (Table 2). The mean baseline ASDAS-CRP and CRP levels were significantly higher in r-axSpA patients, whereas the mean BASDAI was significantly higher in nr-axSpA patients. Physical function, HRQoL and activity impairment were comparable between the r-axSpA and nr-axSpA populations (Table 2).

Within the nr-axSpA population, 393 patients were in the imaging arm, and 114 were in the clinical arm. In general, the characteristics in these arms were similar with the exception that in the clinical arm, a higher proportion of patients were HLA-B27 positive and had a higher mean number of SpA features, as expected according to the ASAS criteria (Supplementary Table S3, available at *Rheumatology* online).

Comparison of demographic and SpA characteristics of axSpA patients between geographic regions

Most axSpA patients were from Europe (62%), followed by China and Latin America. Patients from China were

FIG. 1 Flowchart of patient selection for the analysis
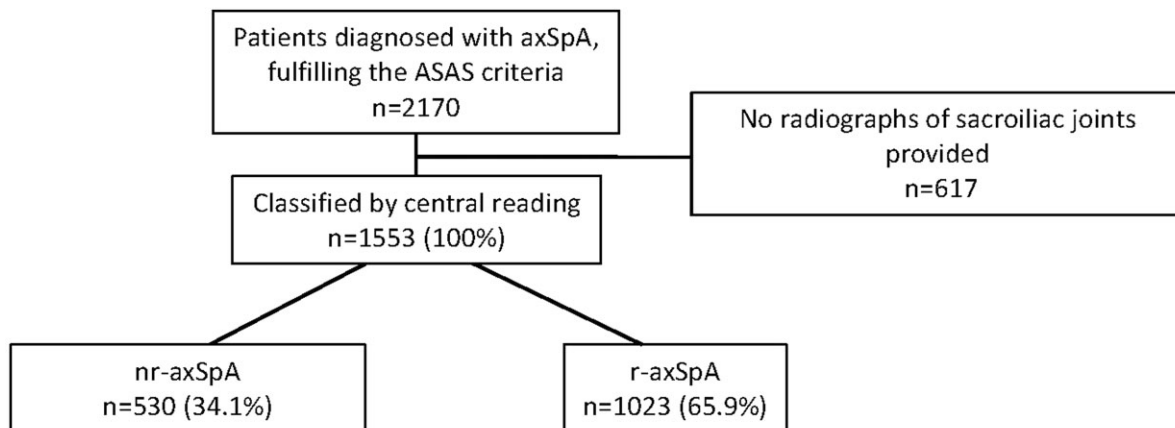
TABLE 1 Demographics and SpA features at baseline in patients with axSpA in PROOF

Characteristics	Overall (*N* = 1553)	nr-axSpA (*n* = 530)	r-axSpA (*n* = 1023)	*P*-value[a]
Age, years, mean (s.d.)	34.7 (10.5) (*n* = 1536)	35.3 (9.6) (*n* = 523)	34.4 (11.0) (*n* = 1013)	0.0943
Male, *n* (%)	983 (63.3)	257 (48.5)	726 (71.0)	**<0.0001**
Symptom duration, months, mean (s.d.)	56.4 (82.1)	48.1 (67.6)	60.8 (88.3)	**0.0017**
SpA features[b], *n*, mean (s.d.)	3.7 (1.4)	3.6 (1.4)	3.8 (1.4)	**0.0022**
HLA-B27 positive[c], *n* (%)	836 (64.6) (*n* = 1295)	251 (56.0) (*n* = 448)	585 (69.1) (*n* = 847)	**<0.0001**
Inflammatory back pain, *n* (%)	1477 (95.1)	501 (94.5)	976 (95.4)	0.4473
Peripheral arthritis, *n* (%)	503 (32.4)	167 (31.5)	336 (32.8)	0.5940
Enthesitis (heel), *n* (%)	553 (35.6)	211 (39.8)	342 (33.4)	**0.0128**
Dactylitis, *n* (%)	87 (5.6)	31 (5.8)	56 (5.5)	0.7606
Uveitis, *n* (%)	151 (9.7)	48 (9.1)	103 (10.1)	0.5234
Psoriasis, *n* (%)	106 (6.8)	52 (9.8)	54 (5.3)	**0.0008**
IBD, *n* (%)	40 (2.6)	23 (4.3)	17 (1.7)	**0.0016**
Good response to NSAIDs, *n* (%)	944 (60.8)	318 (60.0)	626 (61.2)	0.6481
Family history of SpA, *n* (%)	291 (18.7)	100 (18.9)	191 (18.7)	0.9247
Elevated CRP, *n* (%)	718 (46.2)	172 (32.5)	546 (53.4)	**<0.0001**
Active sacroiliitis on MRI, *n* (%)	580 (37.3)	282 (53.2)	298 (29.1)	**<0.0001**

[a]For r-axSpA *vs* nr-axSpA. [b]SpA features included in the ASAS classification criteria for axSpA excluding imaging. [c]Based on patients with HLA-B27 assessed. Significant results in bold.

TABLE 2 Treatment, disease activity and PROs at baseline in patients with axSpA in PROOF

Characteristics	Overall (*N* = 1553)	nr-axSpA (*n* = 530)	r-axSpA (*n* = 1023)	*P*-value[a]
Current treatment, *n* (%)				
NSAIDs	1204 (77.5)	414 (78.1)	790 (77.2)	0.6905
csDMARDs	489 (31.5)	157 (29.6)	332 (32.5)	0.2548
MTX	100 (6.4)	38 (7.2)	62 (6.1)	0.3985
SSZ	366 (23.6)	115 (21.7)	251 (24.5)	0.2116
csDMARDs, other	73 (4.7)	17 (3.2)	56 (5.5)	**0.0454**
Systemic corticosteroids	119 (7.7)	39 (7.4)	80 (7.8)	0.7457
Analgesics	235 (15.1)	93 (17.5)	142 (13.9)	0.0559
TNF inhibitors	234 (15.1)	57 (10.8)	177 (17.3)	**0.0006**
Disease activity/PRO measures, mean (s.d.)				
CRP, mg/L	15.6 (23.0) (*n* = 1361)	11.7 (19.7) (*n* = 467)	17.6 (24.3) (*n* = 894)	**<0.0001**
ASDAS-CRP	2.9 (1.1) (*n* = 1314)	2.8 (1.1) (*n* = 449)	3.0 (1.1) (*n* = 865)	**0.0048**
BASDAI	4.5 (2.3) (*n* = 1543)	4.8 (2.4) (*n* = 526)	4.3 (2.3) (*n* = 1017)	**0.0002**
PtGA	4.9 (2.8) (*n* = 1507)	5.0 (2.9) (*n* = 512)	4.8 (2.7) (*n* = 995)	0.1585
BASFI	3.3 (2.5) (*n* = 1537)	3.4 (2.5) (*n* = 524)	3.3 (2.5) (*n* = 1013)	0.7978
SF-12v2 PCS	40.8 (8.8) (*n* = 1535)	40.6 (8.8) (*n* = 525)	40.9 (8.8) (*n* = 1010)	0.5384
SF-12v2 MCS	44.8 (10.4) (*n* = 1535)	44.2 (10.7) (*n* = 525)	45.1 (10.2) (*n* = 1010)	0.1234
WPAI-SHP presenteeism[b]	35.6 (27.8) (*n* = 826)	37.3 (27.9) (*n* = 293)	34.7 (27.7) (*n* = 533)	0.2008
WPAI-SHP absenteeism[b]	19.3 (32.9) (*n* = 877)	19.3 (32.8) (*n* = 313)	19.3 (33.0) (*n* = 564)	0.9771
WPAI-SHP TWPI[b]	40.3 (29.7) (*n* = 783)	41.6 (29.6) (*n* = 279)	39.6 (29.7) (*n* = 504)	0.3666
WPAI-SHP TAI	43.6 (27.7) (*n* = 1526)	44.8 (28.2) (*n* = 519)	43.0 (27.5) (*n* = 1007)	0.2446

[a]For r-axSpA *vs* nr-axSpA. [b]Analysed among patients currently employed. MCS, mental component summary; PCS, physical component summary; PRO, patient-reported outcome; TAI, total activity impairment; TWPI, total work productivity impairment; WPAI-SHP, Work Productivity and Activity Impairment Questionnaire–Specific Health Problem. Significant results in bold.

the youngest (mean age 29 years; Table 3). Across regions, the r-axSpA:nr-axSpA ratio varied from ~1.5 in Europe, Canada and Latin America to 3.0 in Arabia and 4.2 in China (Table 3). HLA-B27 positivity was more frequent among patients from China (80%) and less frequent among patients from Arabia (29%). Among all axSpA patients, symptom duration was shortest in China and longest in Canada. Significant differences were observed between the regions in the occurrence of peripheral manifestations and EMMs. The highest occurrence of peripheral arthritis (60%), enthesitis (52%) and dactylitis (12%) was in Latin America and was lowest in Canada (9%, 9% and 2%, respectively). The occurrence of uveitis (18%) and psoriasis (14%) was highest in

Canada and lowest in China (6% and <1%, respectively). IBD was highest in Arabia (21%), and no cases were observed in China (Table 3). Although patient numbers were small ($n = 14$), notable findings in South Africa included the highest occurrences of peripheral arthritis (64%), enthesitis (71%) and uveitis (21%) in patients with axSpA across the regions.

Comparison of disease activity and treatments between regions

Patients in Latin America and Arabia had the highest ASDAS-CRP, BASDAI and BASFI scores and China had the lowest (all $P < 0.0001$; Table 4). Most WPAI scores were highest and SF-12 scores lowest in Arabia. Significant differences were also observed in the treatments between regions. The use of MTX, SSZ and corticosteroids was highest in Latin America, analgesics in Europe and TNF inhibitors in Arabia and China (Table 4). NSAID use was ≥72% in all regions except in Arabia (38%). In South Africa, the use of NSAIDs [13/14 (93%)], analgesics [9/14 (64%)], SSZ [8/14 (57%)], corticosteroids [7/14 (50%)] and MTX [4/14 (29%)] was highest vs other regions, while the use of TNF inhibitors and other DMARDs was 0%.

An analysis of covariance confirmed that geographic regions exhibited different frequencies of EMMs (uveitis, $P < 0.01$; psoriasis, $P < 0.0001$) and peripheral arthritis ($P < 0.0001$) independent from other factors (age, sex, symptom duration, HLA-B27 positivity, BASDAI, CRP and csDMARD and TNF inhibitor use).

Comparison of demographics and SpA characteristics in r-axSpA and nr-axSpA patients between geographic regions

Among nr-axSpA patients, the occurrence of psoriasis and IBD varied significantly across regions. IBD was observed most frequently in Canada and Arabia, but not in China. Psoriasis was reported in Canada, but not in China and Arabia (Supplementary Table S4, available at *Rheumatology* online). Among r-axSpA patients, significant differences in the occurrence of peripheral musculoskeletal manifestations (arthritis and enthesitis) and EMMs were also shown, with the highest occurrence in Latin America (Supplementary Table S4, available at *Rheumatology* online). Disease activity, reflected by ASDAS-CRP and BASDAI scores, was higher in Latin America and Europe, respectively, among nr-axSpA patients and higher in Arabia among r-axSpA patients. Among nr-axSpA and r-axSpA populations, the use of MTX, SSZ and analgesics varied substantially across regions (Supplementary Table S4, available at *Rheumatology* online). Significant differences in the use of TNF inhibitors were observed across regions in the r-axSpA population only (highest use in Arabia and China).

Although limited by small patient numbers (seven patients each for nr-axSpA and r-axSpA populations), notable findings for patients from South Africa included the highest occurrences of enthesitis (86%) and peripheral arthritis (86%) for patients with nr-axSpA and the highest occurrences of uveitis (29%) and psoriasis (14%) for patients with r-axSpA across the regions. Additionally, the use of MTX (29% and 29%), SSZ (57% and 57%), analgesics (57% and 71%) and corticosteroids (29% and 71%) was generally higher than across the other regions among the South African nr-axSpA and r-axSpA populations, respectively.

Discussion

The PROOF study is a large multicountry observational study of patients with axSpA conducted at rheumatology clinical practices across six geographic regions [Europe, Arabia, South Africa, North America (Canada only), Latin America and Asia (China only)]. The study enrolled patients with recently diagnosed (≤1 year) axSpA who fulfilled the ASAS classification criteria for axSpA. The majority of patients were classified as having r-axSpA (66%) at baseline by central reading, and only 17% of patients were reclassified. This may reflect a higher confidence among investigators in diagnosing and enrolling axSpA patients that had structural changes in the SI joints.

The PROOF data confirmed known differences between r- and nr-axSpA populations from previous studies [7, 14–16]. Among r-axSpA, the majority of patients were men, whereas both genders were more equally represented in the nr-axSpA population; however, differences between regions were observed. Also in line with previous observations, CRP levels were higher in patients with r-axSpA than nr-axSpA; this was also evident across regions [7, 14–16]. The overall clinical burden of disease (ASDAS-CRP and BASDAI), functional status (BASFI), HRQoL (SF-12v2), work ability (WPAI-SHP) and PtGA were comparable between the two axSpA populations at baseline and consistent with previous observations [15, 17–23]. Although BASDAI (4.8 vs 4.3) and ASDAS-CRP (2.8 and 3.0) differences were significant between nr-axSpA and r-axSpA populations at baseline in PROOF, these differences are not considered clinically relevant [24].

Interestingly, the nr-axSpA population had a higher occurrence of enthesitis, psoriasis and IBD compared with the r-axSpA population. These findings are partially consistent with some previous studies [10, 14]. A meta-analysis of eight observational studies reported a similar prevalence of peripheral manifestations and EMMs among patients with r-axSpA and nr-axSpA, except for a significantly higher pooled historical prevalence of enthesitis among patients with nr-axSpA and a higher pooled historical prevalence of uveitis among patients with r-axSpA [10]. In general, the prevalence (current and past) of peripheral manifestations and EMMs in PROOF was similar compared with the meta-analysis. However, the prevalence of uveitis was lower in PROOF (range among r- and nr-axSpA, 9–10%) vs the meta-analysis (16–23%) and a recent report (22%) [10, 25].

TABLE 3 Baseline patient demographics and disease symptoms of axSpA patients between the different regions

Characteristics	axSpA in different regions (N = 1553)					Overall
	Europe [n = 958 (61.7%)]	China [n = 370 (23.8%)]	Latin America [n = 131 (8.4%)]	Canada [n = 56 (3.6%)]	Arabia [n = 24 (1.5%)]	ANOVA/ chi-squared P-value[a]
Age, years, mean (S.D.)	36.3 (10.5)	29.4 (8.7)	35.7 (10.5)	37.5 (10.2)	36.3 (9.1)	**<0.0001**
Male, n (%)	570 (59.5)	277 (74.9)	84 (64.1)	28 (50.0)	18 (75.0)	**<0.0001**
r-axSpA, n (%)	594 (62.0)	299 (80.8)	71 (54.2)	34 (60.7)	18 (75.0)	**<0.0001**
r-axSpA:nr-axSpA ratio	1.6	4.2	1.2	1.5	3.0	**<0.0001**
Symptom duration, months, mean (S.D.)	61.6 (87.0) (n = 944)	35.1 (49.5)	54.8 (79.2) (n = 128)	100.1 (108.1)	48.7 (57.9)	**<0.0001**
SpA features[b], n (%)	3.7 (1.4) (n = 776)	3.7 (1.3) (n = 360)	4.0 (1.6) (n = 81)	3.1 (1.0) (n = 49)	3.1 (1.3) (n = 17)	**<0.0001**
HLA-B27 positive[c], n (%)	447 (57.6) (n = 776)	289 (80.3) (n = 360)	55 (67.9) (n = 81)	30 (61.2) (n = 49)	5 (29.4) (n = 17)	**<0.0001**
Inflammatory back pain, n (%)	908 (94.8)	357 (96.5)	127 (96.9)	49 (87.5)	23 (95.8)	0.0803
Peripheral arthritis, n (%)	286 (29.9)	118 (31.9)	78 (59.5)	5 (8.9)	7 (29.2)	**<0.0001**
Enthesitis (heel), n (%)	374 (39.0)	84 (22.7)	68 (51.9)	5 (8.9)	12 (50.0)	**<0.0001**
Dactylitis, n (%)	55 (5.7)	13 (3.5)	16 (12.2)	1 (1.8)	1 (4.2)	**0.0080**
Uveitis, n (%)	92 (9.6)	22 (5.9)	22 (16.8)	10 (17.9)	2 (8.3)	**0.0013**
Psoriasis, n (%)	82 (8.6)	2 (0.5)	11 (8.4)	8 (14.3)	1 (4.2)	**<0.0001**
IBD, n (%)	28 (2.9)	0	3 (2.3)	4 (7.1)	5 (20.8)	**<0.0001**
Good response to NSAIDs, n (%)	614 (64.1)	217 (58.6)	66 (50.4)	26 (46.4)	12 (50.0)	**0.0042**
Family history of SpA, n (%)	190 (19.8)	57 (15.4)	24 (18.3)	10 (17.9)	4 (16.7)	0.1126
Elevated CRP, n (%)	453 (47.3)	179 (48.4)	55 (42.0)	17 (30.4)	6 (25.0)	**0.0257**

[a]Interaction P-value assessing the effect of region; South Africa was included in this analysis but data are omitted from the table due to the small number of patients (n = 14). [b]SpA parameters included in the ASAS classification criteria for axSpA excluding imaging. [c]Based on patients with HLA-B27 assessed. ANOVA, analysis of variance. Significant results in bold.

TABLE 4 Baseline treatments, disease activity and PROs of axSpA patients between the different regions

Characteristics	axSpA in different regions (N = 1553)					Overall ANOVA/ chi-squared P-value[a]
	Europe [n = 958 (61.7%)]	China [n = 370 (23.8%)]	Latin America [n = 131 (8.4%)]	Canada [n = 56 (3.6%)]	Arabia [n = 24 (1.5%)]	
Current treatment, n (%)						
NSAIDs	764 (79.7)	266 (71.9)	110 (84.0)	42 (75.0)	9 (37.5)	**<0.0001**
csDMARDs	255 (26.6)	156 (42.2)	63 (48.1)	3 (5.4)	3 (12.5)	**<0.0001**
MTX	50 (5.2)	22 (5.9)	23 (17.6)	1 (1.8)	0	**<0.0001**
SSZ	193 (20.1)	115 (31.1)	47 (35.9)	2 (3.6)	1 (4.2)	**<0.0001**
csDMARDs, other	18 (1.9)	50 (13.5)	3 (2.3)	0	2 (8.3)	**<0.0001**
Systematic corticosteroids	89 (9.3)	5 (1.4)	17 (13.0)	1 (1.8)	0	**<0.0001**
Analgesics	191 (19.9)	5 (1.4)	22 (16.8)	4 (7.1)	4 (16.7)	**<0.0001**
TNF inhibitors	121 (12.6)	90 (24.3)	12 (9.2)	4 (7.1)	7 (29.2)	**<0.0001**
Disease activity/PRO measures, mean (s.D.)						
CRP, mg/L	15.0 (22.2) (n = 868)	15.3 (21.4) (n = 321)	23.4 (33.0) (n = 98)	9.9 (15.4) (n = 50)	24.2 (38.9) (n = 11)	**0.0057**
ASDAS-CRP	3.1 (1.1) (n = 823)	2.5 (1.0) (n = 321)	3.2 (1.3) (n = 97)	2.7 (1.0) (n = 50)	3.0 (1.7) (n = 11)	**<0.0001**
BASDAI	4.8 (2.3) (n = 949)	3.3 (1.9) (n = 369)	5.0 (2.8)	4.3 (2.0)	5.7 (2.3)	**<0.0001**
PtGA	5.2 (2.8) (n = 917)	3.8 (2.3) (n = 369)	5.2 (3.2) (n = 130)	5.2 (2.6)	5.6 (3.2) (n = 22)	**<0.0001**
BASFI	3.8 (2.5) (n = 948)	1.8 (1.8) (n = 368)	4.1 (2.7) (n = 130)	3.2 (2.4) (n = 54)	4.7 (2.6) (n = 23)	**<0.0001**
SF-12v2 PCS	40.1 (8.7) (n = 943)	42.5 (8.0) (n = 369)	40.3 (9.8)	42.2 (10.6)	38.1 (8.9) (n = 22)	**0.0002**
SF-12v2 MCS	43.8 (10.5) (n = 943)	46.5 (9.3) (n = 369)	46.4 (10.8)	48.1 (11.0)	39.4 (12.0) (n = 22)	**<0.0001**
WPAI-SHP presenteeism[b]	38.6 (28.1) (n = 508)	28.7 (24.9) (n = 181)	32.5 (28.8) (n = 77)	32.6 (27.6) (n = 38)	49.2 (31.8) (n = 12)	**0.0006**
WPAI-SHP absenteeism[b]	16.5 (31.4) (n = 527)	28.6 (37.5) (n = 216)	17.9 (30.8) (n = 84)	10.3 (20.5) (n = 32)	16.6 (34.1) (n = 8)	**0.0002**
WPAI-SHP TWPI[b]	41.7 (29.9) (n = 477)	37.8 (28.6) (n = 180)	37.0 (30.7) (n = 76)	40.6 (29.9) (n = 32)	53.7 (30.6) (n = 8)	0.3967
WPAI-SHP TAI	47.1 (28.0) (n = 936)	34.1 (23.3) (n = 369)	43.8 (30.8)	41.4 (26.6)	63.8 (30.4) (n = 21)	**<0.0001**

[a]Interaction P-value assessing the effect of region; South Africa was included in this analysis but data are omitted from the table due to the small number of patients (n = 14). [b]Analysed among patients currently employed. ANOVA: analysis of variance; MCS: mental component summary; PCS: physical component summary; PRO: patient-reported outcome; TAI: total activity impairment; TWPI: total work productivity impairment; WPAI-SHP: Work Productivity and Activity Impairment Questionnaire–Specific Health Problem. Significant results in bold.

The mean duration of symptoms at baseline was 48 months in nr-axSpA and 61 months in r-axSpA in PROOF, and the short disease duration may be associated with the lower prevalence of uveitis, considering that an increased risk of uveitis has been shown to be associated with longer disease duration [26].

Some of the differences compared with historical data can be explained by the geographic heterogeneity of the PROOF study, with some remarkable regional patterns. For example, we observed substantial variation in HLA-B27 positivity, confirming published data reporting a low prevalence of HLA-B27 in axSpA patients from the Middle East and North Africa (54%) [25] and Arab populations (26%) [27], in the Turkish Erciyes Spondyloarthritis Cohort (ESPAC; 45%) [21] and in Brazil (undifferentiated SpA, 61%) [28]. Interestingly, HLA-B27 positivity was also low in Europe in the PROOF study (58%). HLA-B27 positivity rates as high as 95% among patients with AS have been reported, compared with $\leq$8% in most general populations [29, 30]. When comparing the occurrence of SpA features between regions, it was interesting that the peripheral features (peripheral arthritis, enthesitis and dactylitis) were most common in Latin America while the prevalence of uveitis and psoriasis was highest in Canada. At the same time, the prevalence of IBD was highest in Arabia. These differences might be related to the differences in lifestyle and in treatment patterns; for example, greater use of csDMARDs was reported in Latin America (48.1%). The results reflect the frequent use of csDMARDs and glucocorticoids (either oral or by local injection) among patients with peripheral joint disease, in accordance with the current ASAS-EULAR recommendations [31]. Disease activity and physical function impairment were lowest in China, which might be associated with the youngest mean age, shortest symptom duration and greater use of TNF inhibitors in China. However, it is unknown what percentage of the TNF inhibitor users were treated with etanercept, which is not effective for IBD.

Our findings are overlapping and confirm the results of a recently published large multinational observational study characterizing musculoskeletal involvement in patients with SpA, including axSpA, particularly with respect to a higher prevalence of peripheral manifestations and EMMs in Latin America *vs* other geographic regions [25]. In addition, a smaller multinational observational study reported clinical characteristics and patient-reported outcomes across geographic regions; however, no data on EMMs or disease activity were provided [32]. Additional evidence is mostly related to meta-analyses of different European cohorts (German cohort, GESPIC [22]; Turkish cohort, ESPAC [21]; French cohort, DESIR [17]; Swiss cohort, SCQM [18]; Spanish cohort, ESPeranza [33]; Dutch cohort, SPACE [20]). As in other observational studies, it is possible that the frequencies of the peripheral manifestations and EMMs have been influenced by various treatments; of note, both past and current presence of manifestations was taken into account in PROOF. Also, data on disease activity and other patient-reported outcomes should be interpreted in the context of differences in access to expensive treatment options. The PROOF study recruited patients prior to the introduction of IL-17 inhibitors to the market; therefore, no information on this drug class was reported.

One of the strengths of this study is the worldwide coverage and the large number of participating centres that offer the possibility to compare the different areas and countries of the world. Moreover, in this study, the final r-axSpA or nr-axSpA classification per the modified New York criteria was based on a combination of local and central reading of radiographs. Limitations of this observational study are related to substantial differences in the number of patients from different regions, with a small number of patients recruited in Arabia and South Africa. Furthermore, the investigational sites were not selected by a standardized method; therefore, data from each region may not be entirely representative of a larger axSpA population in that region. Also, no information on multidisciplinary collaboration between rheumatology, gastroenterology, dermatology and ophthalmology departments was collected. This could be a limitation for the interpretation of the study results because interdisciplinary collaboration may influence the diagnosis and treatment of EMMs. A total of 617 patients were excluded from the study due to a lack of SI radiographs, which could have potentially introduced a bias. Indeed, the region distribution and some patient characteristics were different in the excluded and included populations, most likely reflecting differences in the routine clinical practices in the covered regions, e.g. using MRI as the first imaging method and refraining from performing radiographs if MRI is positive.

Conclusions

In conclusion, the PROOF study is a large observational, prospective, worldwide study of patients with axSpA. The baseline data provided novel insights into the differences in the clinical presentation of axSpA across various geographic regions. Most notably, patients in Latin America had the highest frequencies of peripheral arthritis, enthesitis and dactylitis, while patients in China had the lowest disease activity, including a low occurrence of peripheral manifestations and EMMs. These data may inform management patterns and the planning of interventional clinical trials.

Acknowledgements

Data availability statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g. protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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