**Rheumatic &
Musculoskeletal
Diseases**

ORIGINAL RESEARCH

Prevalence and distribution of peripheral musculoskeletal manifestations in spondyloarthritis including psoriatic arthritis: results of the worldwide, cross-sectional ASAS-PerSpA study

Clementina López-Medina [1,2,3] Anna Molto [1,2] Joachim Sieper [4]
Tuncay Duruöz,[5] Uta Kiltz [6] Bassel Elzorkany,[7] Najia Hajjaj-Hassouni [8]
Ruben Burgos-Vargas,[9] José Maldonado-Cocco,[10] Nelly Ziade [11]
Meghna Gavali,[12] Victoria Navarro-Compan,[13] Shue-Fen Luo,[14] Sara Monti [15]
Kim Tae-Jong,[16] Mitsumasa Kishimoto,[17] F M Pimentel-Santos,[18] Jieruo Gu,[19]
Ruxandra Schiotis,[20,21] Floris A van Gaalen [22] Pál Geher,[23] Marina Magrey,[24]
Sebastián E Ibáñez Vodnizza [25] Wilson Bautista-Molano [26]
Walter Maksymowych,[27] Pedro M Machado [28,29,30] Robert Landewé,[31,32]
Desirée van der Heijde [22] Maxime Dougados[1,2,33]

ABSTRACT

Objectives To characterise peripheral musculoskeletal involvement in patients with spondyloarthritis (SpA) including psoriatic arthritis (PsA), across the world.
Methods Cross-sectional study with 24 participating countries. Patients with a diagnosis of axial SpA (axSpA), peripheral SpA (pSpA) or PsA according to their rheumatologist were included. The investigators were asked which diagnosis out of a list of six (axSpA, PsA, pSpA, inflammatory bowel disease-associated SpA, reactive arthritis or juvenile SpA (Juv-SpA)) fitted the patient best. Peripheral manifestations (ie, peripheral joint disease, enthesitis, dactylitis and root joint disease), their localisation and treatments were evaluated.
Results A total of 4465 patients were included (61% men, mean age 44.5 years) from four geographic areas: Latin America (n=538), Europe plus North America (n=1677), Asia (n=975) and the Middle East plus North Africa (n=1275). Of those, 78% had ever suffered from at least one peripheral musculoskeletal manifestation; 57% had peripheral joint disease, 44% had enthesitis and 15% had dactylitis. Latin American had far more often peripheral joint disease (80%) than patients from other areas. Patients with PsA had predominantly upper limb and small joint involvement (52%).
Hip and shoulder involvement was found in 34% of patients. The prevalence of enthesitis ranged between 41% in patients with axSpA and 65% in patients with Juv-SpA. Dactylitis was most frequent among patients with PsA (37%).
Conclusion These results suggest that all peripheral features can be found in all subtypes of SpA, and that

Key messages

What is already known about this subject?
► Peripheral musculoskeletal manifestations are a hallmark of psoriatic arthritis (PsA) and occur also in spondyloarthritis (SpA), but their distribution and worldwide prevalence have sparsely been studied in SpA and specifically in axial SpA (axSpA).

What does this study add?
► This study demonstrates that all types of peripheral musculoskeletal manifestations can be found in all subtypes of SpA.
► This study allowed to directly compare the worldwide SpA (including PsA) population across the different geographic areas, and demonstrated a high inter-region variability in the prevalence of these manifestations.
► There is a large overlap of peripheral manifestations across the different SpA subtypes, suggesting a high prevalence of peripheral features in axSpA and quite similar prevalences in peripheral SpA and PsA.

How might this impact on clinical practice or future developments?
► This study suggests that SpA constitutes one entity with different phenotypic presentations (including PsA).
► This study confirms that peripheral musculoskeletal manifestations should be studied in the entire group of SpA rather than in its subgroups alone.

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differences are quantitative rather than qualitative. In a high proportion of patients, axial and peripheral manifestations coincided. These findings reconfirm SpA clinical subtypes are descendants of the same underlying disease, called SpA.

INTRODUCTION

Spondyloarthritis (SpA) mainly affects the axial skeleton and sacroiliac joints but may affect peripheral structures too.[1] Peripheral involvement has always been important in the nomenclature of the diverse forms of SpA. The traditional classification includes several subtypes, such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-associated SpA, reactive arthritis (ReA) and juvenile SpA (Juv-SpA), depending on the presence of peripheral and/or extra-musculoskeletal manifestations.[1] In 2009, the Assessment of Spondyloarthritis international Society (ASAS) has introduced the concept of axial (axSpA) and peripheral SpA (pSpA) and developed new classification-criteria making this distinction.[2] In parallel, and independently, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has proposed specific criteria for the classification of PsA.[3] Guided by the reality of drug development in the field, the US Food and Drug Administration and the European Medicine Agency have proposed specific guidance for drug development limited to three (four) diseases (axSpA (radiographic and non-radiographic (AS)), pSpA and PsA), which to some extent ignores the reality of SpA as an umbrella entity. This pleiotropy has created dilemmas in the field, since patients with peripheral manifestations, that can occur across the entire spectrum of patients with SpA, may easily meet the criteria for more than one disease at the same time, or alternatively may fit distinct criteria over time. Similarly, patients with a SpA-associated diagnosis characterised by peripheral involvement may also present with axial symptoms. Finally, it is suggested that distributions of peripheral manifestations of SpA may differ across geographical areas. It is well known, for example, that the prevalence of peripheral arthritis in Latin American patients with SpA is higher than in Europe[4 5] and that peripheral involvement of SpA in Asia is rather low.[6]

The study of phenotypical distributions has classically evolved along the axes of scientific and professional organisations (eg, GRAPPA vs ASAS), which focused on either peripheral or axial involvement. In addition, ASAS classically had a European dominance, while GRAPPA had a solid North American basis. Moreover, in the majority of previous SpA cohorts, these manifestations (either axial or peripheral) were used as entry criterion, limiting the evaluation of the whole SpA spectrum. These distinctions imply and explain why a thorough comparison of peripheral manifestations in the SpA spectrum, with involvement of countries around the world, has never been conducted so far. This has prompted us to design the ASAS-PerSpA study, which aimed at comparing the prevalence, characteristics and treatments of peripheral musculoskeletal manifestations in patients with all possible subtypes of SpA across all regions of the world. The investigators were also interested to see how often peripheral and axial manifestations in patients with a SpA diagnosis coincide, and if there are global differences.

METHODS

Study design

PerSpA was a multinational observational, cross-sectional study with 24 participating countries worldwide.

Patient recruitment

For this study, the scientific committee appointed one national principal investigator (an ASAS member) for each participating country. Several countries per continent were selected and the national principal investigators invited rheumatologists from their countries to participate. Consecutive adult patients (ie, at least 18 years old) with a diagnosis of axSpA, pSpA or PsA, who were able to understand and complete questionnaires, were included from July 2018 to February 2020.

Data collection

A specific case report form was used to collect four different categories of data:

1. *Demographics:* country, age, sex, body mass index, smoking, alcohol intake and the highest level of education completed.

2. *Disease characteristics:* the investigators were asked to name the diagnosis that in their opinion best described the disease of the patient irrespective of the fulfilment of any classification criteria. They could choose from the following list: axSpA, PsA, pSpA, IBD-related SpA, ReA, Juv-SpA or they could name another disease.
   In addition, information about HLA-B27 status, first-degree or second-degree relatives (with AS, psoriasis, uveitis, ReA or IBD), axial involvement (defined with the question "Do you consider that this patient has ever suffered from axial involvement of SpA?"), information concerning the presence of sacroiliitis on radiographs, uveitis, psoriasis confirmed by a dermatologist, IBD confirmed by endoscopy and treatment (non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional synthetic (cs) and biological (b) disease-modifying antirheumatic drugs (DMARDs)) were collected.

3. *Peripheral musculoskeletal manifestations:* included (a) peripheral joint disease (excluding root joints) in the past, the presence of objective signs of synovitis (ie, physical examination by a rheumatologist or confirmed by ultrasonography), a monoarticular, oligoarticular or polyarticular pattern, localisation (predominantly in the lower limbs/large joints) and natural history (transient, continuous, intermittent or progressive); (b) 'root-joint' (ie, hip and shoulder) involvement in the past according to the rheumatologist, (c) midfoot arthritis (tarsitis) in the past as well

as confirmed by specific investigations; (d) enthesitis in the past confirmed and non-confirmed by specific tests (ie, sonography, radiographs, MRI or bone scintigraphy), localisation and natural history (single episode, intermittent, continuous or progressive) and (e) the occurrence of dactylitis in the past and localisation (fingers or toes) were collected. Moreover, the presence of current peripheral musculoskeletal manifestations at the moment of the study visit was evaluated based on physical examination. Investigators were also asked about specific treatments (NSAIDs, oral and intra-articular glucocorticoids, csDMARDs and bDMARDs) prescribed for each of these peripheral musculoskeletal manifestations using the questions 'Did this manifestation require a specific treatment?' and 'if yes, which one?'

4. *Clinimetric information:* current disease activity at the moment of the study visit was measured by the Bath Ankylosing Spondylitis Disease Activity Index[7] and the Ankylosing Spondylitis Disease Activity Score-C reactive protein (ASDAS-CRP).[8] Moreover, the Ritchie Articular Index,[9] 66 Swollen Joints Index,[10] Mander enthesitis index (MEI),[11] Leeds Enthesitis Index[12] and the Spondyloarthritis Research Consortium of Canada enthesitis score[13] were assessed. The Bath Ankylosing Spondylitis Functional Index and the ASAS Health Index were used to evaluate function and health, respectively.[14 15] Finally, the presence of secondary fibromyalgia according to the rheumatologist's opinion was collected and the self-reported Fibromyalgia Rapid Screening Tool (FiRST) was completed.[16]

All information was obtained by a study investigator or research nurse during a face-to-face interview at one single study visit, which included a review of the medical record. A centralised electronic case report form was used to enter the data.

Statistical analysis

Patients were stratified in four geographic areas: Latin America (Argentina, Chile, Colombia and Mexico), Europe and North America (Canada, France, Germany, Hungary, Italy, Portugal, Romania, Spain, the Netherlands, the UK and the USA), Asia (China, India, Japan, South Korea and Taiwan) and the Middle East and North Africa (Egypt, Lebanon, Morocco and Turkey). North America and Europe were grouped together because the numbers of patients from the USA and Canada were low.

Patients were also grouped according to the best-fit diagnosis (axSpA, PsA, pSpA, IBD-SpA, ReA, Juv-SpA or alternatives). The analysis was purely descriptive. The prevalence of each peripheral musculoskeletal manifestation was estimated and information about such manifestations (locations, natural history and specific treatments) was examined with regard to the geographic area and to the diagnosis.

RESULTS

Demographics and disease characteristics

Investigators from 24 countries recruited a total of 4538 consecutive patients fulfilling the inclusion criteria. Seventy-three patients were excluded because of missing data, and 4465 patients were included in the analysis. The number of patients included per country is summarised in online supplemental table S1. Latin America (12%), Europe and North America (38%), Asia (22%) and the Middle East plus North Africa (29%) were properly represented. North America and Europe were grouped together because the enrolled patients in the USA and Canada were low (only 110 patients). The best-fit diagnoses (in decreasing order) was axSpA (61%), followed by PsA (23%), pSpA (9.7%), SpA-IBD (2.5%), ReA (1.3%), other SpA (1.3%) and Juv-SpA (1.2%). Demographics, clinical characteristics, disease activity and disease burden with regard to the diagnosis are shown in table 1. The prevalence of the HLA-B27 antigen ranged between 18.2% in patients with PsA and 79% in patients with axSpA. Uveitis was found less frequently in patients with PsA (2.6%) and more frequently in patients with axSpA (22%). Patients with PsA had the highest prevalence of psoriasis confirmed by a dermatologist (87%) while patients with ReA and IBD-SpA had the lowest prevalence (3%). Remarkably, 55% of patients with pSpA and 36% of patients with PsA had axial involvement according to the rheumatologist, and 52% of patients with axSpA had ever used csDMARDs. At the moment of the study visit, the prevalence of patients with low disease activity (ASDAS-CRP <2.1) ranged between 36% in pSpA and 41% in axSpA. Online supplemental table S2 shows the same information with regard to the geographic area. HLA-B27 was more frequent among Asian patients (80%) and less frequent among patients from Middle East and North Africa (54%). Asian patients also had the highest prevalence of axial involvement according to the rheumatologist (82%), while only 66% of Latin American patients had axial involvement. Finally, IBD was more prevalent among Middle East and North African patients (8%) and less prevalent among Asian patients (3%).

Peripheral musculoskeletal manifestations

Of all patients, 78% had suffered at least once from a peripheral musculoskeletal manifestation (either peripheral joint disease, root joint involvement, tarsitis, enthesitis or dactylitis). The lowest prevalence was found in axSpA (66%), the highest expectedly in pSpA (99%). The prevalence of musculoskeletal manifestations was plotted against geographic area and diagnosis in figures 1 and 2, respectively. At the moment of the study visit, 32% of patients had at least one current peripheral musculoskeletal manifestation on physical examination (23% of patients with axSpA and 49% of patients with pSpA).

Peripheral joint disease (excluding root joints)

Peripheral joint disease (excluding root joints) was the most frequent peripheral musculoskeletal manifestation

Table 1 Sociodemographics and clinical characteristics, disease activity and disease burden with regard to the diagnosis

	axSpA N=2719	pSpA N=433	PsA N=1033	ReA+IBD-SpA N=168	Juv-SpA+others N=112
Age, mean (SD)	42.0 (13.0)	44.2 (14.4)	51.8 (13.0)	44.8 (14.5)	37.5 (16.6)
Gender (men)	68.3%	46.9%	48.5%	55.4%	61.6%
Region					
Latin America	10.2%	8.1%	17.0%	14.9%	23.2%
Europe and North America	37.2%	23.5%	47.3%	23.8%	30.4%
Asia	22.4%	31.9%	16.0%	20.2%	25.0%
Middle East and North Africa	30.2%	36.5%	19.7%	41.1%	21.4%
BMI (kg/m^2), mean (SD)	25.9 (5.1)	26.3 (5.4)	28.0 (5.9)	25.2 (4.9)	24.1 (4.8)
Ever smoker	1185/2717 (43.6%)	128/432 (29.6%)	494/1032 (47.9%)	36.9%	27.7%
Ever alcohol	1089/2718 (40.1%)	179/432 (41.4%)	451/1032 (43.7%)	36.3%	28.6%
University education	1178/2717 (43.4%)	45.5%	320/1032 (31.0%)	44.0%	41.1%
Fibromyalgia (rheumatologist's opinion)	212/2717 (7.8%)	11.1%	11.6%	9.5%	3.6%
Fibromyalgia (FiRST)	427/2482 (17.2%)	69/391 (17.6%)	245/982 (24.9%)	25/165 (15.2%)	9/107 (8.4%)
Symptom duration (years), mean (SD)	14.4 (11.1)	10.1 (9.5)	16.8 (12.3)	12.7 (10.7)	10.7 (8.8)
Diagnosis delay (years), mean (SD)	5.8 (7.7)	4.3 (6.6)	9.1 (11.1)	6.9 (8.5)	4.0 (6.6)
HLA-B27 positive	1709/2168 (78.8%)	197/316 (62.3%)	86/474 (18.2%)	27/85 (31.8%)	47/77 (61.0%)
First-degree or second-degree relatives of SpA*	35.5%	28.9%	36.3%	22.0%	27.7%
Axial involvement (according to the rheumatologist)	97.5%	55.0%	35.5%	58.3%	66.1%
Sacroiliitis on X-ray	75.1%	33.7%	20.5%	37.5%	48.2%
Uveitis ever	21.6%	17.3%	2.6%	16.1%	18.8%
IBD ever (confirmed by endoscopy)	4.7%	4.4%	0.5%	64.3%	1.8%
Psoriasis ever (confirmed by a dermatologist)	154/2718 (5.7%)	12.2%	86.5%	3.0%	8.9%
csDMARDs ever	51.6%	88.7%	92.8%	92.9%	76.8%
bDMARDs ever	59.3%	51.5%	64.7%	53.0%	48.2%
Current csDMARDs	23.1%	53.1%	59.6%	52.4%	49.1%
Current bDMARDs	47.5%	37.0%	51.6%	38.1%	33.9%
NSAIDs alone	30.5%	15.0%	10.8%	12.5%	23.2%
CRP mg/L, mean (SD)	11.7 (26.6)	13.9 (25.4)	11.4 (28.6)	13.1 (22.5)	12.8 (20.3)
CRP ≥6 mg/L	1142/2295 (49.8%)	48.0%	412/1028 (40.1%)	42.9%	46.4%
ASDAS-CRP, mean (SD)	2.5 (1.1)	2.6 (1.2)	2.6 (1.1)	2.5 (1.1)	2.5 (1.1)
ASDAS-CRP <1.3	457/2682 (17.0%)	67/428 (15.7%)	147/1015 (14.5%)	30/167 (18.0%)	20/110 (18.2%)
ASDAS-CRP <2.1	1088/2682 (40.6%)	153/428 (35.7%)	379/1015 (37.3%)	64/167 (38.3%)	41/110 (37.3%)
PGA, mean (SD)	4.3 (2.7)	4.5 (2.7)	4.6 (2.7)	4.3 (2.7)	4.4 (2.8)
BASDAI, mean (SD)	3.7 (2.4)	4.0 (2.4)	4.3 (2.5)	3.8 (2.4)	3.7 (2.5)
BASFI, mean (SD)	3.0 (2.6)	2.8 (2.6)	3.1 (2.8)	2.8 (2.6)	3.0 (2.7)
ASAS-HI, mean (SD)	6.3 (4.5)	6.6 (4.4)	7.2 (4.7)	6.2 (4.2)	7.4 (4.7)
Peripheral manifestations					
Peripheral joint disease in the past	36.0%	94.7%	90.8%	77.4%	75.9%

Table 1 Continued

	axSpA N=2719	pSpA N=433	PsA N=1033	ReA+IBD-SpA N=168	Juv-SpA+others N=112
Peripheral joint disease in the past confirmed by specific investigations	30.2%	88.9%	85.7%	72.6%	72.3%
Root joints involvement in the past	33.9%	44.3%	26.7%	32.7%	52.7%
Midfoot arthritis (tarsitis) in the past	5.2%	13.6%	10.3%	9.5%	18.8%
Midfoot arthritis (tarsitis) in the past confirmed by specific investigations	1.5%	3.7%	3.1%	3.0%	4.5%
Any enthesitis in the past	40.9%	57.3%	45.8%	45.8%	65.2%
Any enthesitis in the past confirmed by specific investigations	12.9%	25.9%	23.3%	18.5%	27.7%
Dactylitis in the past	6.0%	23.1%	37.0%	12.5%	16.1%
Number of current swollen joints, mean (SD)	0.3 (2.0)	1.2 (2.9)	1.9 (4.8)	0.7 (1.7)	1.1 (6.3)
Any current swollen joint	281/2716 (10.3%)	41.6%	410/1032 (39.7%)	23.8%	24.1%
Number of current tender joints, mean (SD)	1.5 (4.4)	3.3 (6.2)	4.8 (8.7)	2.7 (5.5)	2.1 (5.2)
Any current tender joint	928/2716 (34.2%)	271/433 (62.6%)	651/1032 (63.1%)	53.0%	50.9%
Current MEI score, mean (SD)	2.2 (5.5.)	2.4 (5.7)	2.9 (7.6)	3.0 (6.3)	2.1 (4.4)
Number of current enthesitis according to the MEI†, mean (SD)	0.6 (1.8)	0.6 (2.1)	0.8 (2.7)	0.8 (1.9)	0.7 (1.7)
Any current enthesitis according to the MEI†	455/2716 (16.8%)	18.2%	191/1032 (18.5%)	25.6%	20.5%
Any current enthesitis according to the SPARCC Enthesitis Index	221/2716 (8.1%)	15.2%	143/1032 (13.9%)	16.1%	10.7%
Any current enthesitis according to the LEI	174/2716 (6.4%)	12.2%	106/1032 (10.3%)	10.1%	9.8%

All results are presented as mean and SD and percentages for continuous and categorical variables, respectively.
*First-degree or second-degree relatives with ankylosing spondylitis, psoriasis, uveitis, reactive arthritis or IBD.
†Enthesis with a score >1 according to the MEI.
ASAS-HI, ASAS Health Index; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score; AxSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; FiRST, Fibromyalgia Rapid Screening Tool; IBD, inflammatory bowel disease; IBD-SpA, inflammatory bowel disease-associated spondyloarthritis; SPARCC Enthesitis Index, Spondyloarthritis Research Consortium of Canada Enthesitis Index; Juv-SpA, juvenile spondyloarthritis; LEI, Leeds Enthesitis Index; MEI, Mander Enthesitis Index; PGA, Patient's Global Assessment; PsA, psoriatic arthritis; pSpA, peripheral spondyloarthritis; ReA, reactive arthritis.;

in the whole population with a prevalence of 57% (51% had objective signs of synovitis). The geographical distribution of peripheral joint disease differed importantly: patients from Latin American countries showed the highest prevalence (80%). According to the diagnosis, the lowest prevalence of peripheral joint disease was found in patients with axSpA (36%), while the highest frequency was found in patients with pSpA and PsA (95% and 91%, respectively).

The number of affected joints with regard to diagnosis is illustrated in figure 3. Among the whole population with

peripheral joint disease, 12%, 44% and 44% of patients showed monoarticular, oligoarticular and polyarticular involvement, respectively. But patients with a diagnosis of PsA had predominantly polyarticular involvement (60%), while patients with a diagnosis of ReA or IBD-SpA had predominantly oligoarticular disease (68%). Monoarticular involvement was rare in all groups.

Of all patients with peripheral joint disease, 39% had predominantly lower limb and large joint involvement (figure 4); 31% had only peripheral joint disease of small joints of upper limbs (hands). Interestingly, the prevalence
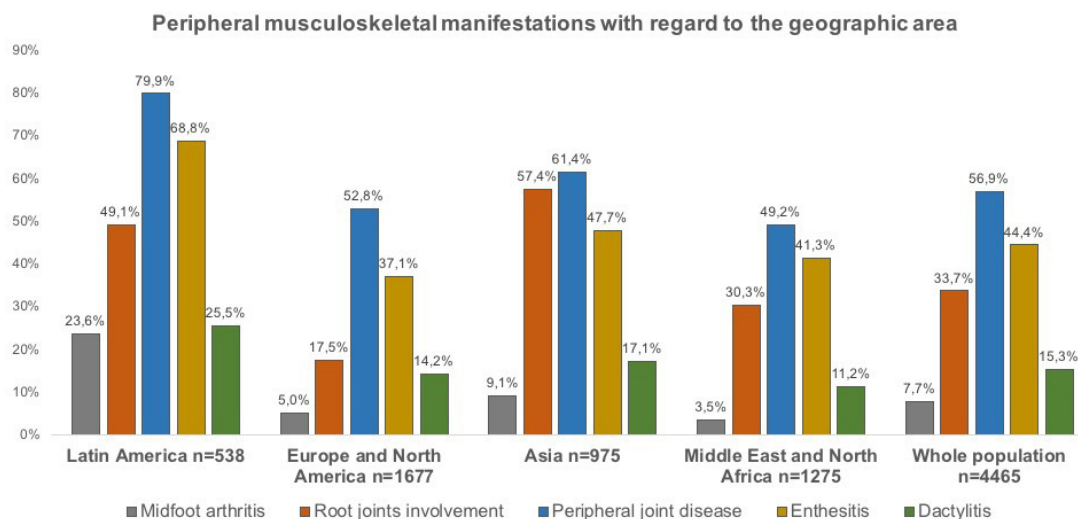
Figure 1 Prevalence of peripheral musculoskeletal manifestations in the past with regard to the geographic area.

of patients with predominantly lower limb and large joint involvement was similar in patients with pSpA (51%) and axSpA (49%). Of the patients with a diagnosis of PsA, 52% had predominantly upper limb and small joint involvement.

Despite the use of bDMARDs at the moment of the study visit was more frequent among patients with axSpA than in pSpA (51.6% vs 47.5%, respectively), patients with pSpA showed the highest prevalence of at least one swollen joint on physical examination (42%) and patients with axSpA showed the lowest prevalence (10%) (table 1).

csDMARDs and bDMARDs specifically for peripheral joint disease were used in 77% and 42% of patients, respectively, while systemic glucocorticoids and local injections were used in 43% and 31%, respectively (table 2).

Root joint involvement

Root joint involvement (ie, hip or shoulder) occurred among all subtypes but ranged between 27% in patients with PsA and 53% in patients with Juv-SpA. Asian patients had most root joint involvement (55%) in comparison with the other regions. Among patients with root joint involvement and available data concerning the location (figure 5), hip involvement alone was found in 57%, being most frequent in axSpA (65%), whereas shoulder involvement alone was found in 21%, being more prevalent in patients with PsA (43%). The highest prevalence of hip and shoulder involvement occurring in the same individual was found in patients with pSpA (32%). Among patients with root joint involvement, 30% initiated bDMARDs specifically for this symptom, while 9% required total articular replacement (table 2).
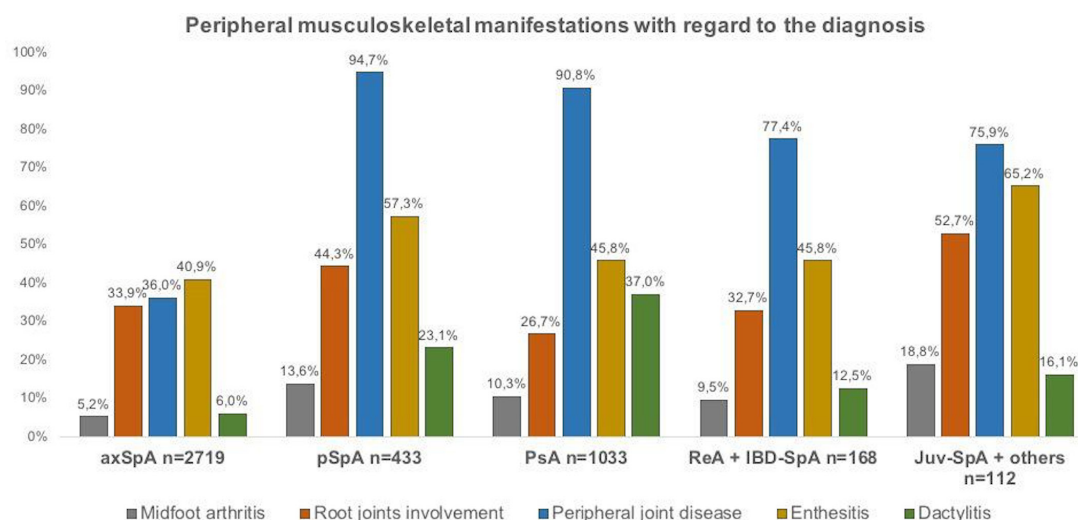
Figure 2 Prevalence of peripheral musculoskeletal manifestations in the past with regard to the diagnosis. axSpA, axial spondyloarthritis; IBD-SpA, inflammatory bowel disease-associated spondyloarthritis; Juv-SpA, juvenile spondyloarthritis; PsA, psoriatic arthritis; pSpA, peripheral spondyloarthritis; ReA, reactive arthritis.

Number of affected joints (excluding root joints) with regard to the diagnosis
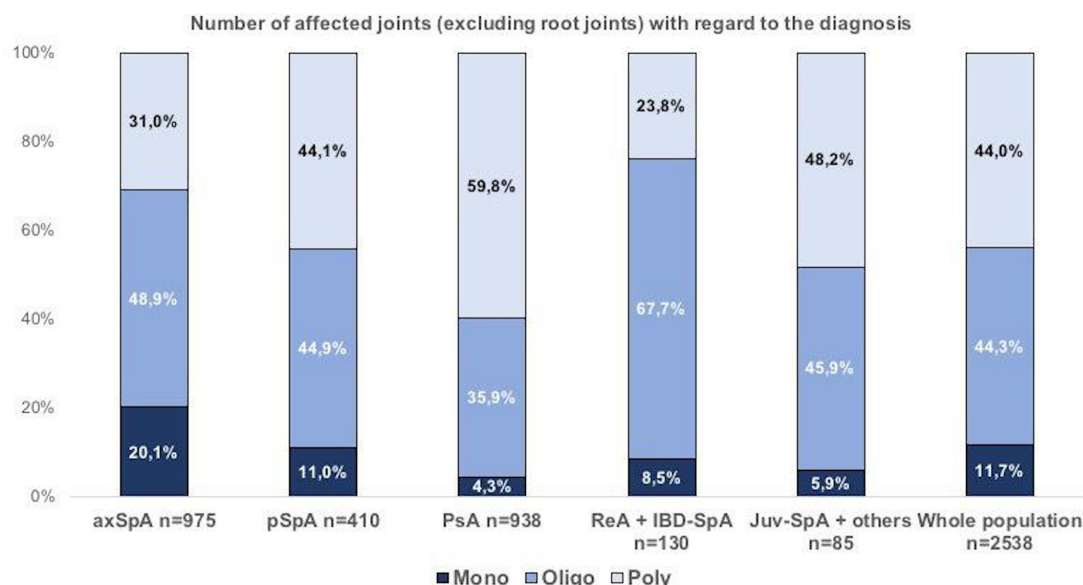
Figure 3 Number of affected joints in the past (excluding root joints) with regard to the diagnosis*. *Among patients with peripheral joint disease (excluding root joints) and available data concerning the number of affected joints (n=2538). axSpA, axial spondyloarthritis; IBD-SpA, inflammatory bowel disease-associated spondyloarthritis; Juv-SpA, juvenile spondyloarthritis; PsA, psoriatic arthritis; pSpA, peripheral spondyloarthritis; ReA, reactive arthritis.

Midfoot arthritis (tarsitis)

A total of 344 patients in the overall population had ever suffered from midfoot arthritis (tarsitis), representing 7.7% (2.2% confirmed by specific investigations). The prevalence of tarsitis ranged between 5.2% in patients with axSpA and 19% in patients with Juv-SpA. With regard to the region, this frequency ranged between 3.5% in Middle East and North African patients and 24% in Latin American patients.

Enthesitis

Of all patients, 44% had ever suffered from any enthesitis (17% had imaging-confirmed enthesitis). Enthesitis was more prevalent in Latin America (61%) than in other countries (approximately 40%). Enthesitis was more prevalent in patients with Juv-SpA (65%) than in other patients (approximately 45%).

The heel (either the insertion of the Achilles tendon or the plantar fascia) was by far the most frequent first

Location of peripheral articular disease (excluding root joints) with regard to the diagnosis
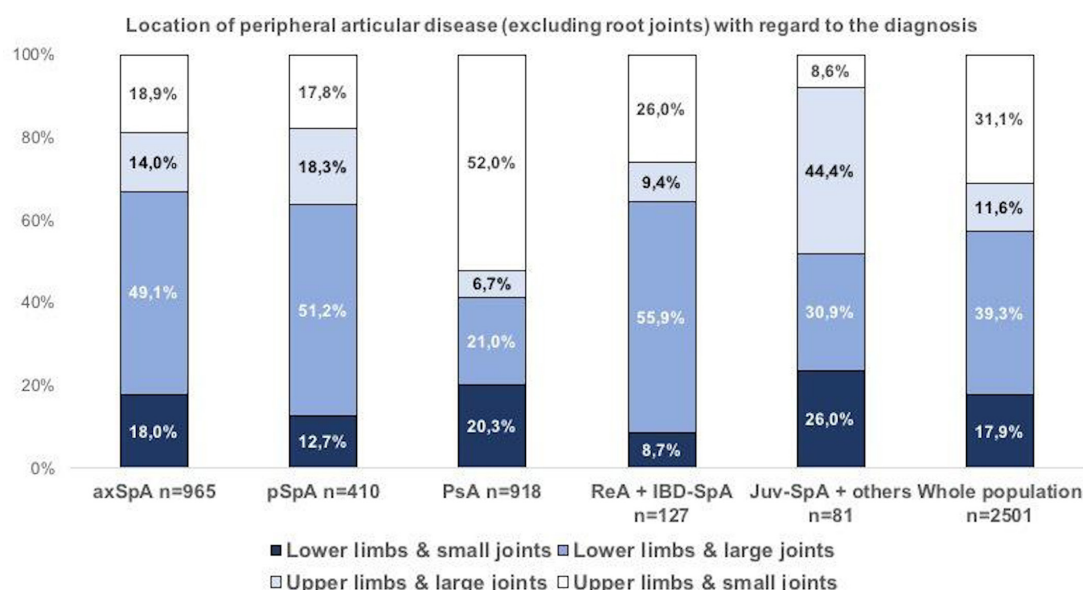
Figure 4 Location of peripheral articular involvement in the past (excluding root joints) with regard to the diagnosis*. *Among patients with peripheral joint disease (excluding root joints) and available data concerning the location of affected joints (n=2501). axSpA, axial spondyloarthritis; IBD-SpA, inflammatory bowel disease-associated spondyloarthritis; Juv-SpA, juvenile spondyloarthritis; PsA, psoriatic arthritis; pSpA, peripheral spondyloarthritis; ReA, reactive arthritis.

Table 2 Specific treatments with regard to each peripheral musculoskeletal manifestation*

	Root joint involvement N=1503	Peripheral joint disease N=2541	Enthesitis N=1984	Dactylitis N=685
NSAIDs	1191 (79.2%)	2317 (91.2%)	1318 (66.4%)	489 (71.4%)
Prescribed for >1 peripheral manifestation	925/1191 (77.7%)	1449/2317 (62.5%)	1052/1318 (79.8%)	467/489 (95.5%)
Systemic glucocorticoids	NC	1100 (43.3%)	289 (14.6%)	NC
Prescribed for >1 peripheral manifestation		235/1100 (21.4%)	235/1984 (11.8%)	
csDMARDs	686 (45.6%)	1962 (77.2%)	665 (33.5%)	377 (55.0%)
Prescribed for >1 peripheral manifestation	561/686 (81.8%)	976/1962 (49.7%)	561/665 (84.4%)	354/377 (93.9%)
bDMARDs	455 (30.3%)	1066 (42.0%)	443 (22.3%)	177 (25.8%)
Prescribed for >1 peripheral manifestation	302/455 (66.4%)	521/1066 (48.9%)	344/443 (77.7%)	164/177 (92.7%)
Local injections glucocorticoids	215 (14.3%)	778 (30.6%)	161 (8.1%)	89 (13.0%)
Prescribed for >1 peripheral manifestation	101/215 (47.0%)	207/778 (26.6%)	83/161 (51.6%)	61/89 (68.5%)
Total articular replacement	136 (9.0%)	20 (0.8%)	NC	NC
Prescribed for >1 peripheral manifestation	4/136 (2.9%)	4/20 (20.0%)		
Any treatment	1251 (83.2%)	2457 (96.7%)	1364 (68.8%)	536 (78.2%)

*Data concerning treatment for midfoot arthritis were not collected.
bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; NC, not collected; NSAIDs, non-steroidal anti-inflammatory drugs.

location for enthesitis (69%). The course of enthesitis (online supplemental figure S1) was intermittent (55%), continuous (21%), monophasic (19%) or progressive (12%). The mean number of locations was 4.3 (4.6), and

slightly higher in patients with a diagnosis of PsA (4.8 (5.3)) (online supplemental figures S2 and S3).

At the moment of the study visit, 18% of patients had enthesitis according to the MEI on physical examination

Location of root joint involvement with regard to the diagnosis
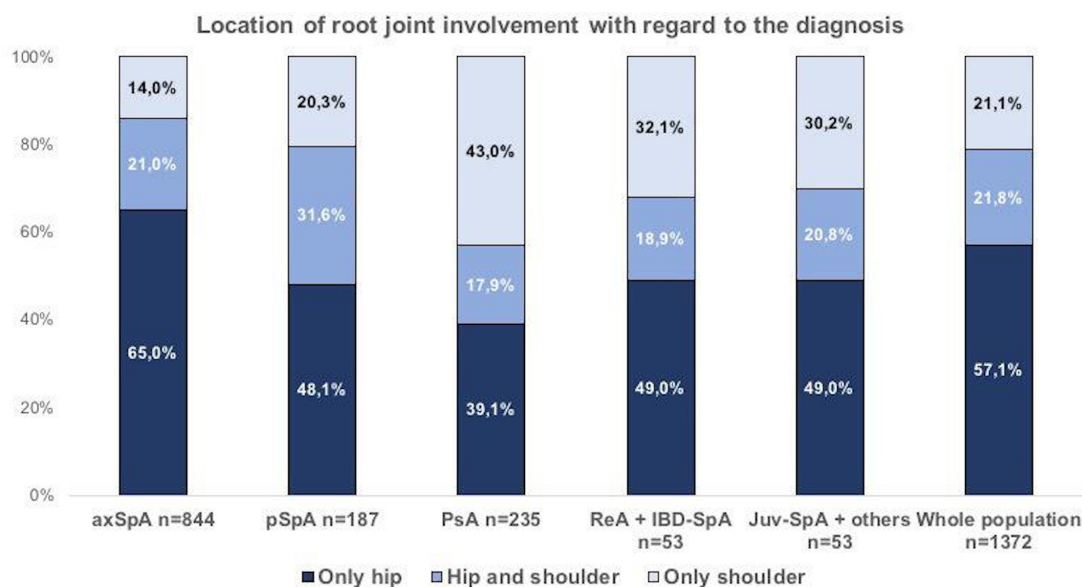
Figure 5 Location of root joint involvement in the past with regard to the diagnosis*. *Among patients with root joint involvement and available data concerning the location (n=1372). axSpA, axial spondyloarthritis; IBD-SpA, inflammatory bowel disease-associated spondyloarthritis; Juv-SpA, juvenile spondyloarthritis; PsA, psoriatic arthritis; pSpA, peripheral spondyloarthritis; ReA, reactive arthritis.

(ie, at least one enthesis with a score >1), less often in patients with axSpA (17%) and more often in patients with ReA and IBD-SpA (26%) (table 1).

The specific treatment used for enthesitis is described in table 2. Remarkably, only 8.1% of patients received local injections with glucocorticoids, and 34% received csDMARDs specifically for this symptom.

Dactylitis

Of all patients, 15% had ever dactylitis. Expectedly, the prevalence was highest in the patients with a diagnosis of PsA (37%) and lowest in patients with axSpA (6%) (figure 1). Dactylitis was slightly more frequent in fingers (62%) than in toes (59%) and occurred in both in 21%. Finger involvement was slightly more prevalent in patients with ReA and IBD-SpA but patients with Juv-SpA had more toe involvement than others(online supplemental figure S4).

Dactylitis was more prevalent in the Latin American countries (26%) than in other regions of the world (approximately 15%).

Concerning treatment, 55% of patients received csDMARDs specifically for dactylitis, 26% bDMARDs and 13% had received local injections of glucocorticoids (table 2).

DISCUSSION

This large multinational study has addressed peripheral musculoskeletal manifestations in patients with diagnoses of the broader spectrum of SpA. Contrary to previous studies that have shown the prevalence of peripheral manifestations about 30%–40% in patients with axSpA, the current study revealed a high prevalence of peripheral manifestations (66%) in these patients. This shows that in spite of the term 'spondyloarthritis', which suggests the spine is the dominant locus of inflammation, peripheral signs and symptoms form an integral part of the phenotype. Another remarkable observation was the high prevalence of axial symptoms found in a study focusing on peripheral manifestations occurring in the broader SpA-spectrum. It is unlikely that this observation reflects selection bias invoked by axSpA experts, since only half of the investigators were ASAS members. It reinforces the suggestion that peripheral and axial manifestations are 'two lots of the same tribe' (the tribe of SpA) and that differences in frequency and distribution determine the clinical diagnosis by the rheumatologist.

The most frequently reported peripheral manifestation was peripheral joint disease (57% of all patients) and the prevalence was roughly similar in both PsA and pSpA (91% and 95%, respectively). This prevalence is similar to that reported in studies focusing on pSpA, in which peripheral arthritis was found in approximately 94% patients.[17 18] Our results confirm previous studies reporting a greater prevalence of peripheral arthritis and enthesitis in patients in Latin America compared with those in European and the Middle East.[5 19] One plausible explanation for this finding

could be, on one hand, the lower prevalence of the HLA-B27 antigen in Latin American populations (60% in Latin Americans vs 80% in Asian patients in our study), which has been classically associated with axial involvement, as well as by the higher prevalence of psoriasis in this geographic area.[20] On the other hand, lifestyle and other factors such as microbiome may play a role in the higher prevalence of peripheral manifestations.[21] HLA-B27 has a low prevalence in both Middle East and North Africa as well as in some Asian countries such as Japan. So, the lower prevalence of HLA-B27 in the Middle East and North Africa was expected. The higher prevalence in Asian countries was likely due to a selection of patients positive for HLA-B27 among the patients seen in clinics. IBD (which is not clearly linked to HLA-B27) was nevertheless higher among patients in the Middle East and North Africa and lower in Asia. This is most likely a finding independent of the prevalence of HLA-B27. Together, these data point to differences between regions in the interpretation of certain SpA features with regard to making a clinical diagnosis.

Peripheral joint disease was mainly oligoarticular and polyarticular involvement and rarely monoarticular. As expected, this distribution differed across diagnoses: polyarticular involvement was more often found in patients with PsA, whereas oligoarticular and monoarticular involvement was most often found in patients with axSpA. In terms of localisation, peripheral joint disease in SpA has classically been considered to occur predominantly in lower limbs and large joints.[22] Unlike previous cohorts, this study had only 39% of patients with peripheral involvement of large joints of lower extremity, which was mainly reported in patients with pSpA, ReA and IBD-SpA. However, patients with PsA had predominantly upper limb and small joints involvement. This means, a predilection of joint involvement is among the most important phenotypical differences between PsA and peripheral SpA, two entities that otherwise seem to be remarkably identical.

Hip involvement is a classical feature in patients with more severe axial disease, which led Amor et al[23] to consider hip involvement as a severity criterion of SpA. These findings gave rise to the hypothesis that hips, together with the shoulders, should be considered 'root joints', behaving more similarly to the spine than to other peripheral joints.[24 25] The majority of studies evaluating hip involvement focused on axSpA, and data for shoulder involvement are scarce. The PerSpA study explored root joint involvement in the whole population of SpA. Overall, not less than 34% reported root joint involvement in the past, especially in Asian participants. Interestingly, the highest prevalence was found in patients with Juv-SpA. Previous studies have also demonstrated that patients with a juvenile onset of SpA (ie, <16 years) are at highest risk of developing hip disease followed by hip replacement.[26] In terms of location, hip involvement alone was found in 57% of those with root joints involved, but hip and shoulder involvement in combination was found in not less than 22% of patients. Expectedly, hip involvement (with or without shoulder involvement) was

highest in patients with axSpA, confirming the known association. But still, half of patients with PsA reported root joint involvement especially shoulder impairment (with or without hip involvement), which nicely fits the observed predominant prevalence of upper limb involvement in this subgroup.

Midfoot arthritis (tarsitis) is a severe involvement of the feet in young people with SpA, especially in the Mexican population.[27–29] Our results confirm these findings: the highest prevalence of tarsitis was reported in Latin American patients as well as in patients with Juv-SpA.

Enthesitis was very prevalent, almost in half. This symptom was more frequent in Latin American patients and less in European and North American patients. Interestingly, enthesitis, a phenomenon historically most associated with axSpA, was lowest in this category and far higher in patients with a diagnosis of PsA. Of note, the percentage of patients with enthesitis that was confirmed by imaging was rather low in all population groups. This highlights that imaging is rarely used to confirm enthesitis, and suggests that pain reported at different locations is often conveniently reported as enthesitis, but may rather be a symptom of widespread pain in the context of general sensitisation (secondary fibromyalgia). Interestingly in this regard, the highest mean number of different locations of all episodes of enthesitis was observed among patients with PsA, which was also the group with the highest prevalence of fibromyalgia according to the FiRST questionnaire. It has been proposed that a subgroup of patients with PsA with 'more enthesitis than synovitis' exists. Indeed, the classification criteria for psoriatic arthritis (CASPAR) recognise 'enthesitis' as a typical clinical feature of this disease by including it as one of the three entry manifestations.[3 30] Due to the overlap between entheseal sites and the classic fibromyalgia tender points, these patients can easily be mixed up with fibromyalgia.

Finally, dactylitis (overall 15%) occurred most frequently in patients with PsA and confirms the view of dactylitis as a hallmark clinical feature of PsA.[31] Classically, dactylitis involves feet more frequently than hands but our findings suggest that this may depend on the subtype of SpA: more than half of patients with ReA and IBD-SpA with dactylitis had dactylitis only of fingers, whereas more than half of patients with Juv-SpA had dactylitis only of the toes.

As expected, csDMARDs and glucocorticoids (either oral or by local injection) were frequently used among patients with peripheral joint disease. These findings are not surprising because, in accordance with the current ASAS-EULAR recommendations, glucocorticoid injections and sulfasalazine may be considered in case of peripheral arthritis.[32] The results for the treatment used for enthesitis partially reflect the current recommendations for associated-PsA enthesitis management,[33] whereby NSAIDs represent the first-line agents. If, indeed, much of the enthesitis reported by patients with PsA (and other SpA) reflects widespread pain rather than inflammation at the insertion of the tendon, this recommendation may lead to overtreatment. Similarly, 34% of patients with enthesitis reported the use of csDMARDs ever, while EULAR and GRAPPA recommendations propose bDMARDs rather

than csDMARDs for 'active enthesitis'.[33 34] Remarkably, clinicians were more concerned about glucocorticoid injections (only 8%), likely explained by the fear for tendon-rupture in weight-bearing entheseal sites.[33]

This study has weaknesses and strengths. One limitation is the cross-sectional design of the study, which does not allow to evaluate cause-effect relationships. The second limitation is the difficulty of precisely evaluating peripheral manifestations that occurred before the actual study visit. This may lead to overcall or underreporting and could not be adjusted for (recall bias). Another limitation, briefly discussed above, is that the proportion of patients with axSpA was larger than that of the other groups, which could have an impact on the overall prevalence of peripheral symptoms in this study. However, this high number of patients with axSpA led us to answer a question which is not really possible to answer based on the available literature,[19] giving a reliable prevalence of peripheral musculoskeletal manifestations in these patients and confirming the necessity of treatment studies focused on these features. The most important strength of this PerSpA study is the worldwide coverage and the large number of participating centres which give the possibility to compare the different regions of the world. Moreover, this study included patients who classically belong to different domains allowing to conduct direct comparisons between entities.

In summary, we have presented here the worldwide clinical picture of peripheral musculoskeletal manifestations in patients with a diagnosis belonging to the entire SpA spectrum. This study suggests that all different peripheral features can be found in all subtypes of SpA (including PsA), and that differences are quantitative rather than qualitative. It also suggests that peripheral and axial manifestations often coincide. Together, these observations reconfirm the overlap between entities in spite of different clinical diagnoses. Our results also confirm the high variability of peripheral musculoskeletal manifestations in patients with SpA worldwide. This first description of the PerSpA cohort will serve as the basis for further ancillary analyses aiming at evaluating the inter-relationship of clinical manifestations and other SpA features, as well as the validity of existing outcome measures.

Author affiliations
[1]Rheumatology Department, Cochin Hospital, Assistance Publique Hôpitaux de Paris, Paris, France
[2]ECAMO, INSERM (U1153): Clinical Epidemiology and Biostatistics, University of Paris, Paris, France
[3]Rheumatology Department, Reina Sofia University Hospital, IMIBIC, University of Córdoba, Córdoba, Spain
[4]Department of Gastroenterology, Infectious Diseases and Rheumatology, Charité University, Berlin, Germany
[5]PMR Department, Rheumatology Division, Marmara University School of Medicine, Istanbul, Turkey
[6]Rheumatology, Rheumazentrum Ruhrgebiet, Ruhr-University Bochum, Herne, Germany
[7]Rheumatology Department, Cairo University, Cairo, Egypt
[8]Rheumatology, Health Sciences College, International University of Rabat (UIR), Rabat, Morocco
[9]Rheumatology Department, Hospital General de México Eduardo Liceaga, Mexico City, Mexico

[10]Rheumatology, Buenos Aires University School of Medicine, Buenos Aires, Argentina

[11]Rheumatology Department, Saint-Joseph University and Mount Lebanon Hospital, Beirut, Lebanon

[12]Department of Rheumatology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

[13]Rheumatology Department, University Hospital La Paz, IdiPaz, Madrid, Spain

[14]Department of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital-Linkou, Taoyuan, Taiwan

[15]Rheumatology Department, Fondazione IRCCS Policlinico S Matteo, University of Pavia, Pavia, Italy

[16]Department of Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, South Korea

[17]Department of Nephrology and Rheumatology, Kyorin University School of Medicine, Tokyo, Japan

[18]Rheumatology, NOVA Medical School, Nova University of Lisbon, Lisboa, Portugal

[19]Rheumatology Department, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

[20]Pharmacology Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

[21]Rheumatology Department, SCBI, Cluj-Napoca, Romania

[22]Rheumatology Department, Leiden University Medical Center, Leiden, The Netherlands

[23]Rheumatology Department, Semmelweis Egyetem, Budapest, Hungary

[24]Rheumatology Department, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

[25]Rheumatology, Facultad de Medicina Clínica Alemana – Universidad del Desarrollo, Santiago, Chile

[26]Rheumatology Department, University Hospital Fundación Santa Fé de Bogotá and Universidad El Bosque, Bogotá, Colombia

[27]Medicine Department, University of Alberta, Edmonton, Alberta, Canada

[28]Centre for Rheumatology and Department of Neuromuscular Diseases, University College of London, London, UK

[29]Department of Rheumatology, University College London Hospitals NHS Foundation Trust, London, UK

[30]Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK

[31]Rheumatology, Amsterdam Rheumatology Center, AMC, Amsterdam, Netherlands

[32]Rheumatology Department, Zuyderland MC, Heerlen, The Netherlands

[33]Rheumatology, Université de Paris Descartes, Paris, France

ORCID iDs
Clementina López-Medina http://orcid.org/0000-0002-2309-5837
Anna Molto http://orcid.org/0000-0003-2246-1986
Joachim Sieper http://orcid.org/0000-0003-0285-9890
Uta Kiltz http://orcid.org/0000-0001-5668-4497
Najia Hajjaj-Hassouni http://orcid.org/0000-0003-0722-6822
Nelly Ziade http://orcid.org/0000-0002-4479-7678
Sara Monti http://orcid.org/0000-0002-1800-6772
Floris A van Gaalen http://orcid.org/0000-0001-8448-7407
Sebastián E Ibáñez Vodnizza http://orcid.org/0000-0002-9577-3078
Wilson Bautista-Molano http://orcid.org/0000-0003-0684-9542
Pedro M Machado http://orcid.org/0000-0002-8411-7972
Desirée van der Heijde http://orcid.org/0000-0002-5781-158X

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