Comparison of the Clinical Expression of Patients with Ankylosing Spondylitis from Europe and Latin America

MARIANA BENEGAS, ELISA MUÑOZ-GOMARIZ, PILAR FONT, RUBEN BURGOS-VARGAS, JOSÉ CHAVES, DANIEL PALLEIRO, JOSÉ MALDONADO COCCO, MIGUEL GUTIÉRREZ, RICARDO SÁENZ, IVAN STECKMEN, OSCAR RILLO, JUAN MULERO, PERCIVAL SAMPAIO-BARROS, ANABELA BARCELOS, BERT VANDER CRUYSSEN, JANITZIA VAZQUEZ-MELLADO, and EDUARDO COLLANTES ESTEVEZ

ABSTRACT. ***Objective.*** To compare the clinical, demographic, and serologic characteristics and the treatment of patients diagnosed with ankylosing spondylitis (AS) from Europe (EU) and Latin America (LA).

Methods. We included 3439 patients from national registries: the Spanish Registry of Spondyloarthritis (REGISPONSER), the Belgian registry (ASPECT), and the Latin American Registry of Spondyloarthropathies (RESPONDIA). We selected patients with diagnosis of AS who met the modified New York classification criteria. Demographic, clinical, disease activity, functional, and metrological measurement data were recorded. Current treatment was recorded. The population was classified into 2 groups: patients with disease duration < 10 years and those with disease duration ≥ 10 years. A descriptive and comparative analysis of variables of both groups was carried out.

Results. There were 2356 patients in EU group and 1083 in LA group. Prevalence of HLA-B27 was 71% in LA group and 83% in EU group ($p < 0.001$). We found a greater frequency of peripheral arthritis and enthesitis ($p < 0.001$) in the LA population; prevalence of arthritis was 57% in LA and 42% in EU, and for enthesitis, 54% and 38%. Except for treatment with anti-tumor necrosis factor (anti-TNF), the use of nonsteroidal antiinflammatory drugs (NSAID), corticosteroids, and disease-modifying antirheumatic drugs (DMARD), and the association of anti-TNF and methotrexate use showed a significant difference ($p < 0.001$) in the 2 populations.

Conclusion. The principal differences in the clinical manifestations of patients with AS from EU and LA were the greater frequency of peripheral arthritis and enthesitis in LA group, the higher percentage of HLA-B27 in EU group, and the form of treatment, with a greater use of NSAID, steroids, and DMARD in the LA group. (J Rheumatol First Release Nov 15 2012; doi:10.3899/jrheum.110687)

Key Indexing Terms:
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Ankylosing spondylitis (AS) is the prototype of seronegative spondyloarthritis (SpA), affecting both the axial and peripheral skeleton, which can also be associated in variable forms to extrarticular manifestations, such as acute anterior uveitis, aortic incompetence, and mucocutaneous and gastrointestinal lesions, among others. The underlying

From the Rheumatology Section, Dr. E. Tornú Hospital, Buenos Aires, Argentina; Rheumatology, Reina Sofia Hospital and Universit/IMIBIC, Córdoba, Spain; Rheumatology, General Hospital of México, México City, Mexico; Rheumatology Hospital, Nacional Edgardo Rebagliati Martins, ESSALUD, Lima, Perú; Rheumatology Section, Instituto Nacional de Reumatología, Montevideo, Uruguay; Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina; Rheumatology, Pontificia Universidad Católica de Chile, Santiago, Chile; Department of Medicine, Division of Rheumatology, Hospital Dr. R.A. Calderón Guardia, San José, Costa Rica; Rheumatology Section, Hospital Universitario de Caracas, Caracas, Venezuela; Rheumatology, H. Puerta de Hierro, Madrid, Spain; División de Reumatología, Faculdad de Medicina, Universidad de São Paulo, São Paulo, Brasil; Rheumatology, Hospital Infante D. Pedro, Aveiro, Portugal; and Department of Rheumatology, Ghent University Hospital, Gent, Belgium.

M. Benegas, MD, Rheumatology Section, Dr. E. Tornú Hospital; E. Muñoz-Gomariz, MD; P. Font, MD, Rheumatology, Reina Sofia Hospital and Universit/IMIBIC; R. Burgos-Vargas, MD, Rheumatology, General Hospital of México; J. Chávez, MD, Rheumatology Hospital, Nacional Edgardo Rebagliati Martins, ESSALUD; D. Palleiro, MD, Rheumatology Section, Instituto Nacional de Reumatología; J. Maldonado Cocco, MD, Instituto de Rehabilitación Psicofísica; M. Gutiérrez, MD, Rheumatology, Pontificia Universidad Católica de Chile; R. Sáenz, MD, Department of Medicine, Division of Rheumatology, Hospital Dr. R.A. Calderón Guardia; I. Steckmen, MD, Rheumatology Section, Hospital Universitario de Caracas; O. Rillo, MD, Rheumatology Section, Dr. E. Tornú Hospital; J. Mulero, MD, Rheumatology, H. Puerta de Hierro; P.D. Sampaio Barros, MD, División de Reumatología, Faculdad de Medicina, Universidad de São Paulo; A. Barcelos, MD, Rheumatology, Hospital Infante D. Pedro; B. Vander Cruyssen, MD, Department of Rheumatology, Ghent University Hospital; J. Vazquez-Mellado, PhD, Rheumatology, General Hospital of México; E. Collantes Estevez, PhD, Rheumatology, Reina Sofia Hospital and Universit/IMIBIC.

Address correspondence to Dr. M. Benegas, Hospital Dr. E. Tornú EX Combatientes de Malvinas, Buenos Aires, 1417 Argentina.
E-mail: mbenegas07@yahoo.com.ar

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pathogenic mechanisms are not fully understood, but their strong associations to genetic[1,2,3] and to a lesser extent, environmental factors[1,2] are widely known. The relationship between HLA-B27 and the SpA, particularly in AS[4,5], suggests its importance in disease susceptibility. Nevertheless, the findings that only 2% of subjects positive for HLA-B27 develop AS[6] and that a small proportion of patients with AS is HLA-B27-negative suggest a genetic predisposition regardless of the HLA-B27 status, as shown in diverse studies[7,8,9]. Environmental factors have been shown to influence not only the etiology, through infections, but also the clinical progression of AS[10] and other SpA.

Some investigators note that ethnic, socioeconomic, and geographic differences influence prevalence and clinical manifestations and prognosis for the SpA[11,12,13], including AS. Migrations between Europe and Latin America have taken place for centuries; do these migratory movements and the subsequent genetic polymorphisms influence the expression of SpA disease? To our knowledge, no comparative population studies have to date evaluated these differences. The objective of our study was to compare the clinical, demographic, and serological characteristics and treatment of European (EU) and Latin American (LA) populations of patients with a diagnosis of AS.

MATERIALS AND METHODS

Patients. We selected 3439 patients from national disease registries: 1422 from the Registry of Spondyloarthritis of the Spanish Society of Rheumatology (REGISPONSER), 847 from the Belgian registry (ASPECT), and 87 from Portugal in the Latin American Registry of Spondyloarthropathies (RESPONDIA). These 3 countries made up the EU group. For the LA group, selected patients were from Brazil, 688 patients; Argentina, 122; Mexico, 100; Chile, 70; Venezuela, 35; Peru, 31; Uruguay, 24; and Costa Rica, 15, all of whom were recorded in the RESPONDIA registry. Patients' characteristics including inclusion and exclusion criteria have been described[14,15,16]. All patients were strictly required to meet the modified New York classification criteria for AS[17].

Data collection. Demographic and associated clinical data including sex, age, age at symptom onset, age at diagnosis, and status for HLA-B27, peripheral arthritis, enthesitis (ever or current) and extrarticular manifestations [uveitis, inflammatory bowel disease (IBD), and psoriasis] were recorded.

Measures of disease status included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), C-reactive protein (CRP), Bath Ankylosing Spondylitis Functional Index (BASFI), AS Quality of Life index (ASQoL), and use of hip prostheses. Metrological measures included the Schöber index, occiput to wall distance, chest expansion, and cervical rotation. Damage was evaluated by the Bath Ankylosing Spondylitis Radiology Index (BASRI), for spine and total damage. Current treatment was recorded including use of nonsteroidal antiinflammatory drugs (NSAID), corticosteroids, and disease-modifying antirheumatic drugs (DMARD), i.e., methotrexate (MTX) and sulfasalazine (SSZ), and anti-tumor necrosis factor (anti-TNF) therapy. Associations between anti-TNF and DMARD use were also recorded.

Statistical analysis. A descriptive analysis of demographic, clinical, serological, and radiological variables of the 2 groups was carried out. A comparative analysis of categorical variables was carried out using chi-square test methods and the Student's t test was used for quantitative variables. CI were calculated for mean and proportional differences.

The study population was classified into 2 groups: patients with disease duration < 10 years and ≥ 10 years. Differences in the variables were evaluated depending on disease progression. Analysis was carried out with SPSS v 18.0; statistically significant differences were considered for p values ≤ 0.05.

RESULTS

The study included 2356 patients in the EU group and 1083 in the LA group; demographic characteristics are shown in Table 1. We found a higher proportion of men in both groups. LA patients were younger than those in the EU group ($p < 0.001$) with a mean difference of 3.5 years (95% CI 2–5 yrs). Positive HLA-B27 status was noted in 570 LA patients, 71% of whom were positive, compared to 83% in the EU group ($p < 0.001$), a mean difference of 11.4% (95% CI 7–15.6).

Comparison of associated clinical characteristics. We found a greater frequency of peripheral arthritis and enthesitis ($p < 0.001$) in the LA population: arthritis was found in 57% of the LA group compared to 42% in the EU group, a mean difference of 15% (95% CI 11.5–18.7). Enthesitis was present in 54% of the LA group and 38% of the EU group, a mean difference 16.8% higher in the LA group (95% CI 13–20). Assessing extraarticular manifestations, we found a higher prevalence of IBD in the EU group than the LA group: 7% vs 4.5%, respectively ($p = 0.007$), mean difference 2.4% (95% CI 0.7–4). We found no differences in other manifestations such as uveitis (EU 24% vs LA 22%; $p = 0.13$) and cutaneous psoriasis (9% in both groups; $p = 0.8$).

Comparison of disease activity and functional indexes. Disease activity measured by BASDAI was slightly greater in the EU group [mean score 4.5 (SD ± 2.3)] than in the LA group [mean score 4.3 (SD ± 2.4); $p = 0.021$]. CRP was similar in both groups ($p = 0.9$). Functional capability measured by BASFI (4.3 ± 2.7 in EU vs 4.8 ± 2.8 in LA) and the percentages of hip prostheses (5% in EU vs 7.8% in LA) proved to be slightly higher in the LA group. In the LA group, however, data for hip prostheses were available for only 386 patients.

Finally, data from the quality of life questionnaire, ASQoL, showed a small difference between the 2 popula-

Table 1. Demographic characteristics of the 3439 patients with ankylosing spondylitis. Results are mean ± SD unless otherwise specified. HLA-B27 in Latin American (LA) cohort calculated in only 570 patients.

Characteristics	EU, n = 2356	LA, n = 1083	p	Mean (95% CI)
Sex male, %	72	75	0.78	2.9 (0.3–6)
Age, yrs	47 ± 12	43 ± 14	< 0.001	3.5 (2–5)
Age at symptom onset, yrs	27 ± 11	28 ± 12	< 0.001	1.5 (0.7–2.4)
Age at diagnosis, yrs	34 ± 12	35 ± 13	0.013	1.3 (0.3–2.3)
HLA-B27, %	83	71	< 0.001	11.4 (7–15.6)

EU: European cohort.

tions ($p < 0.001$), with a score only 1.3 times higher in the LA group: 7 ± 5 in LA compared to 6 ± 5 in the EU group (95% CI 0.7–1.9). Detailed data are given in Table 2.

Comparison of metrological measures. Metrological measurements were found to be slightly higher among the LA group. Cervical limitation was the most relevant finding: 52% in the EU group showed cervical limitation compared to 68% in the LA group [mean difference 8.3% (95% CI 5–11.4); $p < 0.001$]. The chest expansion measure was 3.9 ± 2.0 cm in the EU group and 2.8 ± 2.0 cm in LA, occiput to wall distance 4.8 ± 6 in EU and 6.3 ± 8 in LA, and Schober index 3 ± 1.7 in EU and 2.7 ± 2 in LA.

Radiological involvement was revealed by small differences between the 2 study groups, with mean spinal BASRI score 6.5 in the EU group and 7.0 in the LA group ($p < 0.001$); and total BASRI scores of 7.0 and 8.0, respectively.

Comparison of treatment. We compared patients' treatment at the time of evaluation. Except for treatment with anti-TNF therapy (15% in EU vs 14% in LA), the use of the NSAID, corticosteroids, and DMARD (MTX and SSZ), as well as the anti-TNF and MTX association, showed a significant difference ($p < 0.001$) in the 2 study populations, and the higher percentage was found in the LA group. NSAID were used in 75% of the EU patients but in 89% in the LA group; and corticosteroids 8% versus 19%, MTX 10% versus 34%, and SSZ 19% versus 32%, respectively. In the association of MTX with anti-TNF the difference was 3.5% in the EU group versus 8% in the LA group ($p = 0.001$). These data are detailed in Table 3.

Comparison of metrological characteristics, BASFI, and ASQoL with respect to disease duration (Table 4). The analysis of metrological, functional, and quality of life variables concerning disease duration (< 10 and ≥ 10 years) showed significant differences in every variable in the patients with disease duration under 10 years, with generally higher values in the LA population. In patients with disease duration ≥ 10 years, a significant difference was found only in chest expansion measures (3.7 ± 2.0 in EU vs 3.0 ± 1.9 in LA), BASRI spinal score (7.0 ± 3.0 in EU vs 7.8 ± 3.0 in LA), BASRI total score (8.0 ± 4.0 in EU vs 9.0 ± 4.0 in LA), and ASQoL score (6.7 ± 5.0 in EU vs 7.8 ± 5.0 in LA).

Table 2. Clinical characteristics of patients with ankylosing spondylitis from European (EU) and Latin American (LA) cohorts. Results are mean ± SD unless otherwise specified.

Characteristics	EU	LA	p	Mean (95% CI)
Clinical data				
Arthritis, %	42	57	< 0.001	15 (11–19)
Enthesitis, %	38	54	< 0.001	16.8 (13–20)
Uveitis, %	24	22	0.13	2.3 (0.8–5)
IBD, %	7	4.5	0.007	2.4 (0.7–4)
Psoriasis, %	9	9	0.8	0.2 (1.9–2.4)
Activity and functional index				
BASDAI	4.5 ± 2.3	4.3 ± 2.4	0.021	0.2 (0.03–0.4)
BASFI	4.3 ± 2.7	4.8 ± 2.8	< 0.001	0.48 (0.3–0.7)
CRP	10 ± 21	10 ± 22	0.9	0.15 (1.6–1.8)
ASQoL	6 ± 5	7 ± 5	< 0.001	1.3 (0.7–1.9)
Hip prosthesis, %	5	7.8	0.023	2.8 (0.1–6)
Metrological measurements				
Chest expansion, cm	3.9 ± 2	2.8 ± 2	< 0.001	1 (0.9–1.1)
Occiput to wall distance	4.8 ± 6	6.3 ± 8	< 0.001	1.5 (1–2)
Cervical rotation < 70°	52	68	< 0.001	8.3 (5–11.4)
Schober index, cm	3 ± 1.7	2.7 ± 2	0.002	0.23 (0.08–0.4)
BASRI spinal	6.5 ± 3	7 ± 3	< 0.001	0.65 (0.4–0.97)
BASRI total	7 ± 4	8 ± 4	< 0.001	1.12 (0.8–1.4)

IBD: inflammatory bowel disease; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; ASQoL: Ankylosing Spondylitis Quality of Life score; BASRI: Bath Ankylosing Spondylitis Radiological Index.

DISCUSSION

The results of our study showed that the principal differences in the clinical manifestations of patients with AS from Europe and Latin America are the greater frequency of peripheral arthritis and enthesitis in the LA group, the higher percentage of HLA-B27 in the EU group, and the form of treatment, with greater use of NSAID, steroids, and DMARD in the LA group.

The higher frequency of arthritis and enthesitis in Latin American populations coincides with the findings of a review of SpA in Mexican mestizo patients; that study showed a higher frequency of peripheral arthritis and enthesitis that predominantly involved the lower limbs, especially in juvenile patients, both at onset and during the disease course, compared to white subjects[18,19,20]. In contrast to those results, Lau, *et al* concluded that clinical findings in the surveyed populations (circumpolar populations, Mexican mestizos, Asians, and Africans) were similar to those reported in white subjects[21], and that the prevalence of both peripheral arthritis and spondylitis was similar. Some studies suggest different clinical forms in the different populations studied: in Africa the prevalence was quite different when considering black Africans and North Africans. In black Africans the prevalence was very low, family occurrence was rare, and the disease onset occurred later than in whites[22,23,24]. In contrast, in North Africa AS is

Table 3. Comparison of treatment in patients with ankylosing spondylitis from European (EU) and Latin American (LA) cohorts.

Therapy	EU, %	LA, %	p	Mean (95% CI)
NSAID	75	89	< 0.001	13 (10–17)
Corticosteroids	8	19	< 0.001	11 (7–15)
Methotrexate (MTX)	10	34	< 0.001	24 (19–29)
Sulfasalazine	19	32	< 0.001	13 (8–18)
Anti-tumor necrosis factor (TNF)	15	14	0.6	1 (3–5)
Anti-TNF + MTX	3.5	8	< 0.001	5 (1.6–8)

NSAID: nonsteroidal antiinflammatory drugs.

Table 4. Clinical features in patients with ankylosing spondylitis from European (EU) and Latin American (LA) cohorts categorized by disease duration (< 10 vs ≥ 10 years).

	< 10 Years				≥ 10 Years			
	EU, n = 540	LA, n = 172	p	Mean (95% CI)	EU, n = 1740	LA, n = 195	p	Mean (95% CI)
Chest expansion	4.7 ± 2.3	3.4 ± 1.8	< 0.001	1.3 (1–1.7)	3.7 ± 2	3 ± 1.9	< 0.001	0.7 (0.4-1)
Occiput to wall distance	2 ± 3.8	3.7 ± 6	< 0.001	1.7 (0.7–2.6)	5.6 ± 6.5	6.5 ± 7.5	0.086	0.9 (0.1–2)
Schober	3.7 ± 1.7	3.3 ± 1.7	0.004	0.5 (1.5–0.8)	2.8 ± 1.7	2.8 ± 2	0.65	0.07 (0.2–0.4)
BASFI index	3.4 ± 2.5	4.2 ± 3.1	0.004	0.8 (0.2–1.3)	4.5 ± 2.7	4.9 ± 3	0.168	0.3 (0.1–0.7)
BASRI spinal	4 ± 2	6 ± 3	< 0.001	2 (1.4–2.6)	7 ± 3	7.8 ± 3	0.016	0.7 (0.1–1.3)
BASRI total	4.5 ± 2	7.3 ± 3.7	< 0.001	2.8 (2–3.6)	8 ± 4	9 ± 4	0.002	1.2 (0.4–2)
ASQoL	5 ± 5	7.6 ± 5.5	< 0.001	2.5 (1.6–3.5)	6.7 ± 5	7.8 ± 5	0.002	1.2 (5–2)

Definitions as in Table 2.

frequent and severe, and a high level of familial occurrence is reported. AS occurs much earlier, and there is a high frequency of juvenile AS. Adult disease forms seem to be similar to those reported in white subjects[20,25,26].

Although the literature shows that the extraarticular manifestations are less frequent in black Africans, Asians, Mexicans, and Brazilians[19,22,24,27,28], in our study we found only a small but significant difference (p = 0.007) in the frequency of IBD between the EU and LA groups.

Other differences in our study are the data for activity and function measured using the BASDAI, BASFI, and ASQoL. Although the findings were statistically significant (p < 0.005), we think that the differences are not clinically relevant, because in our daily practice the score of 4.5 in the BASDAI is not different from 4.3. This also appears regarding the data from BASFI (4.3 vs 4.8) and the ASQoL (6 vs 7). A similar situation occurred regarding the percentage of hip prostheses, which was slightly higher in the LA group. However, other studies showed relevant differences in hip involvement: in North African subjects (Algeria, Morocco, and Tunisia) the risk of hip involvement was estimated at 39% after 10 years of disease progression[26], which was much higher than the 14% to 17% estimated in the European patients with AS[25]. The young age at disease onset was important in all cases and was considered key to the risk of hip involvement even in developed countries[29]. In addition, when Moroccan and French patients were compared, the former were found to have more severe disease, with a greater radiological involvement, i.e., 48% compared to 16%, respectively (p < 0.0001)[25].

The metrological findings (clinical and radiological) proved to be different in the 2 study groups, and greater involvement was found in the LA groups in every case. However, on assessment such differences were not significant, because they were < 1 cm; such differences are to be expected when the measurements are carried out by different investigators and, in our opinion, they have no clinical relevance. The involvement of cervical rotation is the only measurement to be highlighted, and this can be supported by studies that found that Mexican mestizos had greater cervical involvement, atlantoaxial subluxation, and ossification of the longitudinal posterior ligament than white subjects[21].

When the populations were classified according to disease duration, statistically significant differences were found in every variable in patients with disease duration < 10 years, and only in the chest expansion, BASRI, and ASQoL measures in patients with disease duration ≥ 10 years. However, the differences were very small and therefore we inferred that there were no differences between the 2 groups regarding disease duration.

The difference between groups regarding HLA-B27 status was to be expected, because frequencies of HLA-B27 vary sharply among the various forms of SpA and among different ethnic groups[5,30]. For example, in healthy individuals, the frequency of HLA-B27 in American blacks ranges from 2% to 4%; in Mexican mestizos it varies between 2% and 5%[31,32]; in Colombia the percentage is under 1%[33]; and in whites it is 8%. The proportion of patients with AS who are negative for HLA-B27 varies from 0% in North American Indians to > 40% in American black and South African populations[34].

Multiple studies show a lower frequency of HLA-B27 in Latin America: for example, in 68% to 80% of Mexican patients[32,35] and 78% of Brazilian patients. In our study the frequency of HLA-B27 was 71% in 570 patients in the LA group and 83% in the EU groups.

Another finding to be noted in our study is a greater tendency to use drugs in the LA group (NSAID, corticosteroids, DMARD). This could be explained by the greater frequency of peripheral involvement in this population, or by different responses to treatment due to differences in pharmacokinetics and in clinical responses, as well as adverse side effects. These speculations cannot be demonstrated by this type of study. Unfortunately, few clinical trials have been carried out on non-white patients and many rheumatologists resort to treatments that have been tested in other populations.

As for limitations to our study, we acknowledge that the use of records may entail errors and omissions in data collection; similarly, the use of extensive cohorts with several researchers can cause differences in the clinical and/or radiological interpretation.

The socioeconomic characteristics of the cohorts were not determined in our study, which could influence the results. Finally, the fact that the population studied is part of the whole population could affect the results.

We note that the Latin American populations have a mixture of Eastern genes of indigenous tribes, a pool of genes from the Spanish and Portuguese populations that settled in the 20th century, and a small black component from the slaves brought by the European conquerors. Differences between our 2 study populations suggest an important role of the genetic background of these populations, modulated by the environment, although these hypotheses must be confirmed with further studies.

APPENDIX

List of study collaborators. The following centers and investigators participated in this study. RESPONDIA group: Alvarellos A, Hospital Privado de Córdoba, Córdoba, Argentina; Asnal C, Hospital Alemán, Buenos Aires, Argentina; Barreira JC, Hospital Británico, Buenos Aires, Argentina; Bernard Medina AG, Hospital F. Antonio Alcalde, Guadalajara, México; Bertolo MB, Universidade de Campinas, Brazil; Bianchi WA, Santa Casa do Rio de Janeiro, Brazil; Bonfiglioli R, Pontifícia Universidade Católica de Campinas, Brazil; Carneiro S, Universidade Federal do Rio de Janeiro, Brazil; Carvalho HMS, Hospital de Base, Brasília, Brazil; Casado GC, Hospital Militar Central, Buenos Aires, Argentina; Casasola Vargas J, Hospital General de México, México City, México; Castro da Rocha FA, Universidade Federal do Ceará, Fortaleza, Brazil; Chacón RL, Policlínica Méndez Gimón, Caracas, Venezuela; Costa IP, Universidade Federal do Mato Grosso do Sul, Campo Grande, Brazil; Duarte AP, Universidade Federal de Pernambuco, Recife, Brazil; Espinoza-Villalpando J, Hospital Regional PEMEX, Reynosa, México; Esteva MH, Hospital Central San Cristóbal, San Cristóbal, Táchira, Venezuela; Fuentealba C, Hospital San Boraja Arriarán, Santiago, Chile; Granados Y, Hospital Núñez Tovar, Maturín Monagas, Venezuela; Huerta-Sil G, CLIDITER, México, México; Keiserman M, Pontifícia Universidade Católica de Porto Alegre, Brazil; Kohem CL, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; Leite NH, Faculdade Souza Marques, Rio de Janeiro, Brazil; Lima SAL, Hospital do Servidor Público Estadual de São Paulo, São Paulo, Brazil; Maldonado-Cocco JA, IREP, Buenos Aires, Argentina; Meirelles ES, Universidade de São Paulo, Brazil; Menin R, Faculdade de Medicina de São José do Rio Preto, Brazil; Neira O, Hospital del Salvador, Santiago, Chile; Paira S, Hospital JM Cullen, Santa Fé, Argentina; Pimentel F, Complexo Hospitalar Egas Moniz, Lisbon, Portugal; Pinheiro M, Universidade Federal de São Paulo, Brazil; Polito E, Santa Casa de Belo Horizonte, Brazil; Resende G, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; Ribeiro SLE, Universidade Federal do Amazonas, Manaus, Brazil; Rillo OL, Hospital Tornú, Buenos Aires, Argentina; Santiago MB, Escola de Saúde Pública da Bahia, Salvador, Brazil; Santos H, Instituto Portugués de Reumatología, Lisboa, Portugal; Scherbarth H, Mar del Plata, Argentina; Sauma MFLC, Universidade Federal do Pará, Belém, Brazil; Skare TL, Hospital Evangélico de Curitiba, Brazil; Sousa E, Complexo Hospitalar Lisboa Norte, Lisboa, Portugal; Spangenberg E, Instituto Nacional de Reumatología, Montevideo, Uruguay; Valin V, Universidade Federal do Espírito Santo, Vitória, Brazil; Vera C, Hospital Luis Vernaza, Guayaquil, Ecuador; Verdejo U, Hospital Carlos van Buren, Valparaíso, Chile; Vieira WP, Hospital Geral de Fortaleza, Brazil; Wong R, S. Plaza, Rosario, Argentina.

The ASPECT study group includes C. Ackerman, V. Badot, P. Bastien, H. Berghs, V. Bonnet, B. Bouchez, Y. Boutsen, J-P. Brasseur, E. Coigne, M. Coppens, L. Corluy, T.F. Cornet, P. Coutellier, S. Daens, A. Silvano Dall', F. Daumerie, G. De Brabanter, V. De Decker, K. Declerck, E. Dhondt, S. Di Romana, C. Docquier, R. Duckerts, L. Dujardin, J-P. Engelbeen, D. Fernandez-Lopez, D. Focan-Henrard, M-A. Fontaine, D. Francois, P. Geusens, G. Ghyselen, S. Goemaere, L. Gyselbrecht, R. Halleux, E. Heuse, A. Heylen, A-M. Huynen-Jeugmans, C. Immesoete, X. Janssens, D. Jardinet, R. Joos, E. Kruithof, C. Langenaken, C. Leens, D. Lefebvre, S. Lefebvre, J. Lenaerts, F. Luyten, K. Maenaut, M. Maertens, B. Maeyaert, H. Mielants, A. Mindlin, M. Moris, A. Nzeusseu, C. Pater, A. Peretz, J. Praet, J. Qu, F. Raeman, R. Reychler, I. Ronsmans, N. Sarlet, G. Schatteman, A. Sileghem, G. Stappaerts, P. Stasse, V. Taelman, L. Tant, F. Toussaint, N. Van Den Bossche, X. Van Mullen, P. Van Wanghe, M. Vanden Berghe, M. Vanden Berghe, J. Vanhoof, A. Verbruggen, L. Verbruggen, W. Verdickt, P. Volders, P. Vroninks, R. Westhovens, L. Williame, M. Wouters, H.G. Zmierczak.

The REGISPONSER study group includes E. Collantes Estévez, H. Reina Sofía; P. Zarco Montejo, H. Fundacion Alcorcón; C. González Fernández, H.G. Marañón, J. Mulero Mendoza, Clínica Puerta Hierro; J.C. Torre Alonso, H. Monte Naranco, J.L. Fernández Sueiro, H.J. Canalejo, J. Gratacós Masmitjá, H. Parc Taulí; X. Juanola Roura, H. Bellvitge; E. Batlle Gualda, Hu Alicante; P. Fernández Dapica, H Doce De Octubre; L.F. Linares; E. Ferrando, H Virgen De La Arrixaca; M.E. Brito Brito, H Ramón Y Cajal; E. Cuende Quintana, Hu Príncipe De Asturias; C. Vázquez Galeano, H.G. San Jorge; E. Calero Secall, Hu Carlos Haya; M.J. Romero Ramos, H sta María Del Rosell; E. Jiménez Ubeda, Hu Miguel Servet; C. Rodriguez Lozano, H. Doctor Negrín; A. García López, H. Virgen Del Rocío; M. Fernández Prada, Hu De Guadalajara; R. Queiro Silva, H Central De Asturias; E. Moreno Ruzafa, H. San Rafael; E. Judez Navarro, H. Virgen Del Perpetuo Socorro; A.J. Más, H. Fundación Son Llatzer; C. Medrano Le Quement, H Internacional Merimar; E. Ornilla, Hu Navarra; C. Montilla Morales, Hu Virgen De La Vega; M. Pujol Busquets, H Mutua De Terrass; T. Clavaguera Poch, H. De Palamos; M.C. Fernández Espartero, H. De Móstoles.

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