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A registry of ankylosing spondylitis registries and prospects for global interfacing

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Abstract

Purpose of review—To review the optimal criteria and conditions for establishing a clinical registry, as well as detailing their application in a number of ankylosing spondylitis (AS) and axial spondyloarthritis (axSpA) Registries already in existence.

Recent findings—Recent genetic studies and studies of long-term treatment efficacy and side-effects have underscored the need for large numbers of patients, much larger than would be possible from a single center or consortium. An optimal Registry should have its aims established upfront, with appropriate governance and oversight, and inclusion and exclusion criteria for participating collaborators and subject defined. Collaborators contributing subjects to a Registry should use validated instruments for which they have been previously trained. The numerous cross-sectional and longitudinal Registries on AS and axSpA have been recently established that differ widely depending on the referral and selection issues.

Summary—The challenge of large-scale examinations of genetics, comorbidities, medication usage, and side-effects in spondyloarthritis underscores the need for combining data from well characterized registries of AS patients which require careful planning. There are currently many such registries available internationally, offering promise for collaborations and data pooling that can answer some of the pressing questions facing rheumatology clinicians and researchers.

Keywords

genetics; patient cohorts; registries; spondyloarthritis; treatment outcome

INTRODUCTION

Strictly speaking, a patient or clinical Registry is defined as ‘an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves (a) predetermined scientific, clinical, or policy purpose(s) [1]’. As such, the term ‘Registry’ can be applied to a variety of settings. This includes cross-sectional or longitudinally followed cohort studies, in which interventions are not being applied, particularly in which long-term follow-up is desirable. In contrast to case–control studies of treatment efficacy, registries are particularly to weigh the effect of potential confounders or treatment combinations or in situations in which placebo-controlled studies might either be unethical or blinding is impractical or in which randomization might be unethical or

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Conflicts of interest

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unnecessary. Registries can be applied effectively to studies of heterogeneous patient populations, because of the much broader inclusion criteria and fewer exclusion criteria that would otherwise be found in randomized clinical trials allowing surveillance for rare events or of rare diseases, or studies of standard of care, or healthcare access and barriers to care. In the last 10–15 years, a number of cohorts and registries of ankylosing spondylitis (AS) or axial spondyloarthritis (axSpA) patients have been established. This review will summarize the components of an optimally established Registry and illustrate these in currently available Registries and longitudinal cohorts.

Before data collection ensues, a group of individuals (an organizing committee) must come together to clearly establish the underlying purpose of the registry to be established (the endpoints), which investigators will constitute the leadership and oversight of the registry, who will be responsible for obtaining funding, and how the data will be collected, preferably by recruiting committed and trained investigators. This committee will also decide who will participate in the data collection and monitoring and which criteria will be used for patient recruitment and data entry, as well as inclusion/exclusion criteria, and mode of data collection and how they should be quantified (if at all). The latter is preferably done with standardized protocols (preferably those that have already been validated elsewhere) for which those contributing data to the study have received standardized training, in order to reduce interobserver variability. These rules are harder to apply in Registries with a large number of sites or clinicians contributing patients, in which standardized training is less feasible and other biases can creep in. Power issues relative to the endpoints being examined should be defined upfront and an appropriate sample size established. The endpoints and data points should also be realistic, collectable within the study budget and feasible in the setting of where the data will actually be extracted (clinics, insurance records, etc.). Issues surrounding retention in and adherence to the study should be addressed, and strategies to deal with the missing data planned upfront. The instruments should be subjected to pilot study to confirm their feasibility within the setting of the actual investigation. Coding manuals and data dictionaries should be employed to not only assure the data are collected uniformly, but also that they are entered and analyzed consistently and accurately.

CURRENT REGISTRIES IN SPONDYLOARTHRITIS

The Registries in spondyloarthritis (SpA) currently in existence generally are of two types. One is the medication-based or treatment-based registry, in which patients with multiple, often related diseases are enrolled to test the efficacy and side-effects of a given medication over time. These are often funded by drug companies or national governments, and are extremely useful in postmarketing surveillance. Examples of this are European Registries such as Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología (BIOBADASER) [2], Reuma.pt (The Rheumatic Diseases Portuguese Registry) [3], NOR-DMARD. The Norwegian DMARD Registry [4] and South Swedish Arthritis Treatment Group Registry [5] contain large numbers of SpA as well as other patients. On the other hand are disease-based registries, either cross-sectional, in which a snapshot of the features of a disease in a large population is desired, or longitudinal, usually focused on endpoints defined at outset (disease progression, treatment efficacy or mortality). The latter will be the focus of this review.

Registro español de espondiloartritis de la sociedad española de reumatología (Tables 1 and 2)

This is a database registry initiated in April 2004 by the Spondyloarthritis Study Group of the Spanish Society of Rheumatology in order to establish a large enough cohort of patients to enable a representative determination of clinical disease features and disease progression, even from onset [6]. All hospital-based and community-based Rheumatology Units in Spain

were invited to participate and maximum dissemination of information regarding the project is carried out among all Spanish. Clinical and demographic characteristics of the AS patients in this cohort are illustrated in Tables 1 and 2 [7].

Registro ibero-americano de espondiloartritis (Tables 1 and 2)

Since 2005, more than 100 university centers from 10 countries have participated in the work group of RESPONDIA (The Ibero-American Registry of Spondyloarthritis). The idea arose with the support of the Spanish Society of Rheumatology (SER), which decided to apply the REGISPONSER protocol in Ibero-American countries [6,7]. The objective was to document demographic data, clinical data, and quality of life. Representative data from this cohort are shown in Tables 1 and 2, in which very large clinical differences are seen between the 10 countries involved, perhaps reflecting differing referral patterns or clinical foci of the contributing sites.

Brazilian Registry of Spondyloarthritis (Table 2)

This is a cross-sectional descriptive study developed at several tertiary healthcare centers in Brazil participating in the Brazilian Registry of Spondyloarthritis (BRS), which represents the five Brazilian geographic macroregions, with patients cared for from January 2006 to December 2009 [7] and including 1472 consecutive patients diagnosed with SpA. The diagnosis of SpA was considered when the patients met the modified New York criteria [8]. Psoriatic arthritis (PsA) was considered when the patients met the Moll and Wright criteria [9]. The diagnosis of ReA was considered when asymmetric inflammatory oligoarthritis of the lower limbs was associated with enthesopathy and inflammatory low back pain after enteric and urogenital infections. Arthritis associated with inflammatory bowel disease (IBD) was considered in the presence of inflammatory axial pain and peripheral articular involvement associated with IBD (Crohn's disease or ulcerative colitis). Juvenile SpA was considered when the SpA symptoms began before the age of 16 years.

German Spondyloarthritis Inception Cohort (Table 3)

This is an ongoing, prospective, longitudinal study on the clinical, functional, and structural outcome of SpA of short duration (inception cohort) [10] set up in 2000 as part of the German Competence Network Rheumatology program and involves four university hospitals, five community hospitals, and four private practices. Focused mainly on patients with axial disease, German Spondyloarthritis Inception Cohort (GESPIC) includes both patients with AS and patients with nonradiographic axial SpA. Patients included in GESPIC are required to have a definite clinical diagnosis of axial SpA according to the treating rheumatologist. Patients with axial SpA were further classified by the local rheumatologist based on the radiographic findings, irrespective of the presence of concomitant psoriasis or IBD, as having either AS or nonradiographic axial SpA. The classification of AS was based on fulfillment of the modified New York criteria [8], and the duration of symptoms was restricted to or less than 10 years at the time of inclusion. The classification of nonradiographic axial SpA was based on fulfillment of the European Spondyloarthropathy Study Group criteria [11], with minor modifications, and the maximum duration of symptoms was or less than 5 years. Radiographs of the spine and sacroiliac joints were obtained at baseline and after 2 years. Data from this cohort are presented in Table 3.

The Egyptian Spondyloarthritis Registry

This is a descriptive, multicenter, cross-sectional study including consecutive patients with SpA diagnosed according to the European spondyloarthritis study group criteria [11] aimed at characterizing socioeconomic features, disease activity and functional status, treatment use, and quality of life in a cohort of Egyptian population by standard instruments. Four

Egyptian centers participated (one from the Upper Egypt, one from the Delta, and two from the West Coast), collecting data over a 12-month period on 75 patients, of whom 34 had AS (64%), 23 patients PsA (45.3%), 15 patients juvenile onset AS (18.7%), 2 patients with reactive arthritis (2.7%), and 1 with inflammatory bowel disease related arthritis (1.3%) [12].

The Spondyloarthritis Research Consortium of Canada Registry for spondyloarthritis (Table 4)

This is a network of Canadian investigators interested in spondyloarthritis supported by The Arthritis Society [13] aimed at addressing the genetic basis of susceptibility of the disease and developing and validating clinical and imaging outcomes to assess disease activity and structural damage over time, the response to therapy, and the clinical burden of illness in terms of quality of life and disability.

The Spondylitis Association of America (SAA) Spondyloarthritis Research and Treatment Network (SPARTAN)/Program to Understand the Longterm Outcomes in Spondyloarthritis registry

This is a new registry comprising three established North American longitudinal cohorts: the Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS), the Toronto University Health Network Spondylitis Program, and the Program to Understand the Longterm Outcomes in Spondyloarthritis (PULSAR) Registry.

PSOAS [14■] is a NIH funded study based at four academic medical centers in the United States followed longitudinally since 2002. As of January 2013, 961 patients had been enrolled (mean age 45 ± 14 years, 70.1% men, 81% white, 84.3% HLA-B27 positive, 32.2% with uveitis, 5.6% IBD, 11% psoriasis, and 45% on anti-TNF agents) of whom over 600 are still being longitudinally followed, with extensive standardized clinical, psychological, and sociodemographic instruments applied at each study visit, and genetic, serologic, and radiographic data collected and analyzed.

The Toronto University Health Network Spondylitis Program cohort (also participating in the SPARCC Registry), longitudinally followed on protocol since 2001, is a longitudinal observational cohort with prognostic, clinical, and translational research embedded [15]. Similar data have been collected as PSOAS cohort, and approximately 800 AS patients have been enrolled (mean age 41 ± 13 years, 76.4% men, 77.5% white, 80% HLA-B27 positive, 25.6% with uveitis, 13% IBD, 7% psoriasis, and 48% on anti-TNF agents).

PULSAR was initiated in 2007 to better characterize the clinical and pathophysiologic aspects of SpA in U.S. veterans. To date, 434 patients have been enrolled (mean age 59.1 years, 93% men, 72% white, 31% HLA-B27 positive, 23% AS, 35% PsA, 6% with uveitis, 3% IBD-associated SpA, 2% undifferentiated spondyloarthritis, and 42% on anti-TNF agents).

Outcome Assessments in Ankylosing Spondylitis International Study

This cohort is an international, longitudinal, observational historical cohort on outcomes in AS [16] comprised 217 consecutive Dutch, French, and Belgian patients with AS (of whom 85.3% were HLA-B27 positive) established in 1996 and followed into the next decade. All patients were TNF-Naïve, most having been treated primarily with NSAIDs alone and were felt to represent the spectrum of AS seen in practice at the time. The Outcome Assessments in Ankylosing Spondylitis International Study (OASIS) cohort was used as the comparison cohort for assessing the radiographic progression in most of the anti-TNF trials, including etanercept [17], infliximab [18], and adalimumab [19].

Devenir dEs spondyloarthropathies récentes

This large, national, multicenter, longitudinal, prospective follow-up of patients aged over 18 and less than 50 years from 25 regional centers in France presenting with early inflammatory back pain (IBP) was established by the French Society of Rheumatology in order to set up a database to facilitate several investigations on diagnosis, prognosis, epidemiology, pathogenesis, and medico-economics in the field of early IBP and SpA. Patients are being recruited if they have IBP of more than 3 months and less than 3 years, and are followed every 6 months during the first 2 years then every year during at least 5 years [20]. Data collected include demographics, disease activity, severity, comorbidities, socio-economics, treatments, radiological and MRI evaluation of the spine and the pelvis according to the local investigators. The recruitment period of the 708 patients (mean age: 34 ± 9 years, women 54%, HLA-B27 positive 57%) in the 25 centers was 26 months (from December 2007 to April 2010). The modified New York criteria, Amor criteria, ESSG criteria, and axial Assessment of SpondyloArthritis international Society (ASAS) criteria were fulfilled by 26, 77, 76, and 67% of the patients at entry, respectively. A history or current symptoms suggestive of peripheral arthritis, acute anterior uveitis, and inflammatory bowel disease were observed in 21, 9, and 4% of the patients, respectively.

Spondyloarthritis Caught Early cohort (Table 5)

Patients with chronic (almost daily) back pain for at least 3 months but less than 2 years, with the onset more than 45 years visiting the rheumatology outpatient clinic in the Leiden University Medical Centre, have been included in the Spondyloarthritis Caught Early (SPACE) cohort – an observational inception cohort including patients with chronic back, since January 2009 [21]. Patients undergo MRI and radiograph of the sacroiliac joints at baseline. Patients were diagnosed as having axSpA if they had IBP (by ASAS expert criteria and at least three SpA features) or if patients had IBP with one or two SpA features and were HLA-B27 positive. Patients with no other SpA features in addition to IBP could only be diagnosed as having axSpA if both HLA-B27 and active sacroiliitis (MRI-SIJ) were present.

Assessment of Spondyloarthritis International Society cohort (Table 6)

The ASAS cohort was compiled for the validation of the new classification criteria for axSpA. Patients with chronic back pain of at least 3 months with onset less than 45 years and with a suspicion of SpA but without a definite diagnosis were included and assessed according to a fixed protocol by rheumatologists who are experts in the field of SpA [22]. Assessments included past or current SpA features, C-reactive protein, and HLA-B27 typing. Plain radiographs of the pelvis were taken in all patients. The local rheumatologist and radiologist assessed sacroiliitis on standard radiograph [8] and the presence or absence of typical signs of active inflammation on pelvic MRI.

The Observation Study of Korean Spondyloarthropathy Registry cohort (Table 6)

This is an ongoing, longitudinal, observation study on the clinical, functional, and structural outcome of spondyloarthritis in Korea [23] supported by the Korean Ministry for Health, Welfare, and Family Affairs. It includes patients meeting the modified New York criteria for AS. Clinical data included age, sex, duration of disease, age at onset of AS symptoms, family history of AS, history of uveitis and iritis, peripheral arthritis, enthesitis, and HLA-B27 carrier status, as well as functional capacity (BASFI).

CONCLUSION

The Registry concept is an optimal method to study the manifestations, prevalence, or outcomes in large heterogeneous populations of a given disease or exposure. Optimally applied, registries use strictly defined goals, endpoints, and standardized, validated methodologies that can be realistically applied by a motivated and well trained group of investigators or observers. The numerous registries and cohort studies in AS and SpA in the recent years illustrate both the benefits of careful preplanning as well as some of the problems with local heterogeneity because of potential confounders. However, with the development of research technologies and treatments needing long-term studies of outcome and monitoring for rare complications beyond what is possible in a clinical trial or single cohort study, the need for such large-scale, long-term analyses that well designed and implemented Registries has never been greater.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 556).

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KEY POINTS

- Registries are ideally organized systems using observational study methods to collect uniform clinical and other data to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, in order to serve predetermined scientific, clinical, or policy purpose(s).
- Registries can be applied effectively to studies of heterogeneous patient populations, because of the much broader inclusion criteria and fewer exclusion criteria characteristic of randomized clinical trials allowing surveillance for rare events, studies of standard of care, healthcare access, and barriers to care.
- What is key in establishing a Registry are clear goals established upfront, an oversight committee that establishes funding, policies and procedures and inclusion and exclusion criteria as well as a motivated and pretrained group of investigators using standardized and validated instruments to collect a realistic dataset.
- A number of cohort studies and registries have been established in SpA over the last 15 years, especially in the last 5 years, which differ widely in their composition, often depending on their initial aims, referral patterns, and inclusion criteria.

Table 1

Comparison of the clinical expression of patients with AS from Europe and Latin America from the REGISPONDER and RESPONDIA cohorts

Characteristics	EU, n=2356	LA, n=1083	P value	Mean (95% CI)
Demographic data				
Sex male, %	72	75	0.78	2.9 (0.3–6)
Age, years	47 ± 12	43 ± 14	<0.001	3.5 (2–5)
Age at symptom onset, years	27 ± 11	28 ± 12	<0.001	1.5 (0.7–2.4)
Age at diagnosis, years	34 ± 12	35 ± 13	0.013	1.3 (0.3–2.3)
HLA-B27, %	83	71	<0.001	11.4 (7–15.6)
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)
Hip prosthesis, %	5	7.8	0.023	2.8 (0.1–6)
BASRI spinal	6.5 ± 3	7 ± 3	<0.001	0.65 (0.4–0.97)
Therapy				
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)
Antitumor necrosis factor (TNF)	15	14	0.6	1 (3–5)
Anti-TNF + MTX	3.5	8	<0.001	5 (1.6–8)

Clinical and demographic data obtained from patients with SpA from the RESPONDIA Study, including patients from REGISPONDER, compared with the values obtained from Brazilian registry of spondyloarthritis

Table 2

	Argentina	Chile	Spain	Mexico	Peru	Portugal	Uruguay	Venezuela	Costa Rica	Brazil
# Patients	405	109	2367	172	60	101	53	69	33	1036
Male (%)	58.8	60.6	68.5	59.3	65.0	58.4	66.0	62.3	57.6	73.6
Age at onset (years)	38.4	35.3	29.6	28	30.6	26.7	31.0	29.4	34.5	31.0
Disease duration (years)	9.7	6.7	18.0	10.1	9.7	19.8	10.2	11.5	6.8	12.7
HLA-B27 (%)	46	n.a.	n.a.	n.a.	31	86	n.a.	n.a.	57	69.5
AS (%)	30.4	58.7	61.5	59.9	53.3	83.2	52.8	55.1	45.5	72.3
PsA (%)	46.7	25.7	17.5	15.1	6.7	11.9	17.0	21.7	0	13.7
ReA (%)	6.4	0.9	1.9	2.9	1.7	3.0	0	0	0	3.6
IBD-associated (%)	0	5.5	1.0	1.7	0	2.0	3.8	4.3	0	1.0
JSpA (%)	1.7	1.8	0.5	0	25.0	0	7.5	4.3	0	3.1
USpA (%)	12.3	7.3	2.1	19.8	13.3	0	18.9	11.6	45.5	6.3
Uveitis (%)	9.9	19.3	16.0	18.6	23.3	33.7	7.5	20.3	12.1	20.2
Enthesitis (%)	32.8	52.3	9.4	79.7	8.3	11.9	52.8	34.8	57.7	24.7
Anti-TNF Tx	10.4	0	0	12.1	1.7	10.8	0	27.0	12.1	5.4

JSpA, juvenile spondylarthritis; PsA, psoriatic arthritis; ReA, reactive arthritis; USpA, undifferentiated spondyloarthritis. Data from Gallinaro *et al.* [7].

Table 3

Baseline demographic and clinical aspects of the GESPIC cohort: a representative axial SpA cohort

Parameter	Nonradiographic axial SpA (n=95)	Ankylosing spondylitis (n=115)	All patients (n=210)
Age, mean $\pm$ SD years	38.7 $\pm$ 9.9	36.8 $\pm$ 11.0	37.1 $\pm$ 10.6
Symptom duration, mean $\pm$ SD years	3.2 $\pm$ 2.2	5.2 $\pm$ 2.8	4.2 $\pm$ 2.7
Duration since diagnosis, mean $\pm$ SD years	1.0 $\pm$ 1.3	2.0 $\pm$ 2.0	1.5 $\pm$ 1.8
Male sex	32 (33.7)	75 (65.2)	107 (51.0)
HLA-B27 positive	69 (72.6)	97 (84.3)	166 (79.0)
Peripheral arthritis	16 (16.8)	15 (13.0)	31 (14.8)
Enthesitis ^a	23 (24.2)	23 (20.0)	46 (21.9)
Uveitis ever	15 (15.8)	27 (23.5)	42 (20.0)
Psoriasis ever	11 (11.6)	17 (14.8)	28 (13.3)
Inflammatory bowel disease ever	1 (1.1)	3 (2.6)	4 (1.9)
Family history of ankylosing spondylitis	16 (16.8)	19 (16.5)	35 (16.7)
BASDAI, mean $\pm$ SD, 0–10	4.2 $\pm$ 2.0	3.8 $\pm$ 2.2	3.9 $\pm$ 2.2
BASFI, mean $\pm$ SD, 0–10	2.8 $\pm$ 2.2	3.0 $\pm$ 2.4	2.9 $\pm$ 2.3
Treatment with NSAIDs	64 (67.4)	76 (66.1)	140 (66.7)
Treatment with DMARDs	26 (27.4)	35 (30.4)	61 (29.0)
Treatment with systemic steroids	6 (6.3)	6 (5.2)	12 (5.7)
Treatment with a TNF α blocker	1 (1.1)	4 (3.5)	5 (2.4)
Smoker, current	24 (25.3)	39 (33.9)	63 (30.0)
Modified SASSS, mean $\pm$ SD	2.30 $\pm$ 4.24	5.86 $\pm$ 10.30	4.25 $\pm$ 8.31
Syndesmophytes	13 (13.7)	35 (30.4)	48 (22.9)

Except where indicated otherwise, values are the number (%) of patients. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; DMARDs, disease-modifying antirheumatic drugs; GESPIC, German Spondyloarthritis Inception Cohort; NSAIDs, nonsteroidal anti-inflammatory drugs; SASSS, Stoke Ankylosing Spondylitis Spine Score; SpA, spondylarthritis; TNF α , tumor necrosis factor α . Data from Rudwaleit *et al.* [10].

^aTwelve enthesitis sites of the lower limbs plus optional sites elsewhere were assessed.

Table 4

Demographic features by disease type in 2028 patients with SpA in the SPARCC database assessed at the first clinic visits after 1 January 2006; database as of 2 February 2010

Characteristics	AS	PsA	ReA	USpA
No. of patients	1108	803	24	93
Age at diagnosis, years, mean $\pm$ SD	30.9 $\pm$ 11.6	37.9 $\pm$ 13.1	31.6 $\pm$ 8.1	30.2 $\pm$ 14.8
Female, <i>n</i> (%)	288 (26.1)	353 (44.0)	11 (50.0)	35 (38.5)
Caucasian, <i>n</i> (%)	913 (87.5)	643 (94.1)	22 (100)	78 (86.7)
Patients with uveitis, <i>n</i> (%)	324 (32.6)	13 (1.6)	5 (20.8)	16 (17.2)
Patients with psoriasis, <i>n</i> (%)	117 (12.4)	429 (68.1)	0 (0)	4 (4.4)
Patients with tender joints, <i>n</i> (%)	201 (34.7)	427 (56.5)	10 (41.7)	26 (28.6)
Patients with swollen joints, <i>n</i> (%)	107 (10.4)	303 (40.1)	4 (16.7)	10 (11.0)
Patients with enthesitis, <i>n</i> (%)	350 (33.3)	171 (23.0)	5 (20.8)	12 (13.6)
Patients with dactylitis, <i>n</i> (%)	19 (1.9)	97 (13.2)	1 (4.3)	2 (2.2)
BASDAI, mean $\pm$ SD	4.7 $\pm$ 2.5	4.1 $\pm$ 2.5	4.5 $\pm$ 2.5	4.2 $\pm$ 2.5
BASFI, mean $\pm$ SD	3.9 $\pm$ 2.8	3.2 $\pm$ 2.7	3.1 $\pm$ 2.8	2.5 $\pm$ 2.6
Presence of comorbidities, <i>n</i> (%)				
Cardiac disease	124 (20.7)	310 (38.8)	3 (12.5)	19 (20.4)
Diabetes	15 (2.5)	86 (10.8)	1 (4.2)	5 (5.4)
Cancer	13 (2.2)	25 (3.3)	0 (0)	2 (2.2)
Trauma	40 (7.1)	80 (10.6)	0 (0)	3 (3.6)
Infection	51 (19.8)	121 (38.8)	9 (69.2)	13 (20.3)
Presence of HLA-B*27, <i>n</i> (%)	715 (79.0)	87 (16.1)	15 (68.2)	53 (63.1)
ESR, mm/h, mean $\pm$ SD	16.4 $\pm$ 17.6	15.3 $\pm$ 16.6	16.8 $\pm$ 24.2	11.1 $\pm$ 11.5
CRP, mg/day, mean $\pm$ SD	11.9 $\pm$ 17.6	9.6 $\pm$ 15.0	16.2 $\pm$ 33.2	7.1 $\pm$ 8.8

JSaA, juvenile spondylarthritis; PsA, psoriatic arthritis; ReA, reactive arthritis; USpA, undifferentiated spondyloarthritis. Data from Gladman *et al.* [13].

Table 5
Baseline characteristics of patients in the SPACE cohort and the ASAS cohort; SpA versus no SpA

	SPACE cohort ^a			ASAS cohort ^a		
	axSpA (n=65)	No SpA (n=92)	P value	axSpA (n=421)	No SpA (n=264)	P value
Age (years) at inclusion, mean ± SD	31.5 ± 16.6	31.1 ± 8.8	0.86	31.0 ± 10.8	35.8 ± 10.5	0.839
Male, n (%)	29 (44.6)	23 (25.0)	0.01	225 (53.4)	87 (33.0)	<0.001
Duration of back pain, mean ± SD	13.4 ± 7.4 (months)	13.7 ± 7.1 (months)	0.79	6.3 ± 7.8 (years)	9.3 ± 10.7 (years)	0.792
HLA-B27 positive, n (%)	44 (67.7)	9 (9.8)	<0.001	270 (64.1)	73 (27.7)	<0.001
Pos. fam. history SpA, n (%)	31 (47.7)	25 (27.2)	0.01	106 (25.2)	52 (19.7)	0.097
IBP, n (%)	52 (80.0)	53 (57.6)	0.003	324 (77.0)	125 (47.3)	<0.001
Psoriasis, n (%)	10 (15.4)	6 (6.5)	0.07	36 (8.6)	13 (4.9)	0.073
Dactylitis, n (%)	4 (6.2)	2 (2.2)	0.20	28 (6.7)	5 (1.9)	0.005
Enthesitis, n (%)	10 (15.4)	15 (16.3)	0.88	86 (20.4)	38 (14.4)	0.046
Uveitis, n (%)	10 (15.4)	5 (5.4)	0.04	43 (10.2)	21 (8.0)	0.323
IBD, n (%)	4 (6.2)	5 (5.4)	0.85	14 (3.3)	4 (1.5)	0.149
Preceding infection, n (%)	2 (3.1)	0 (0.0)	0.09	12 (0.17)	5 (0.14)	0.434
CRP (mg/l), mean ± SD	8.3 ± 11.6	5.7 ± 6.9	0.11	7.1 ± 14.9	2.4 ± 4.4	<0.001
ESR (mm/h), mean ± SD	13.6 ± 16.3	10.4 ± 10.7	0.17	b	b	
Alternating buttock pain, n (%)	15 (23.1)	18 (19.6)	0.60	174 (41.3)	65 (24.6)	<0.001
Good response to NSAIDs, n (%)	27 (41.5)	27 (29.3)	0.11	259 (61.5)	73 (27.7)	<0.001
Elevated CRP/ESR, n (%)	15 (23.1)	16 (17.4)	0.38	170 (40.4)	43 (16.3)	<0.001
Arthritis, n (%)	13 (20.0)	10 (10.9)	0.11	171 (40.6)	59 (22.3)	<0.001
Sacroiliitis radiograph, n (%)	11 (16.9)	1 (1.1)	<0.001	123 (29.2)	9 (3.4)	<0.001
Sacroiliitis MRI, n (%)	27 (41.5)	0 (0.0)	<0.001	202 (48)	8 (3)	<0.001

Data from Van den Berg et al. [21] and Rudwaleit et al. [22]. ASAS, Assessment of SpondyloArthritis international Society; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen; IBD, inflammatory bowel disease; IBP, inflammatory back pain, preceding infection can be balanitis, urethritis, cervicitis, and acute diarrhea; SPACE, Spondyloarthritis Caught Early.

^aDiagnosis according to rheumatologist.

^bNot estimated in ASAS cohort.

Table 6

Demographic and clinical features of AS patients in the OSKAR cohort

Features	Cases
Age, mean $\pm$ SD (years)	33.2 $\pm$ 10.1
Age at onset, mean $\pm$ SD (years)	20.9 $\pm$ 8.1
Duration of disease, mean $\pm$ SD (years)	12.1 $\pm$ 8.1
Male, <i>n</i> (total, %)	732 (830, 88.2)
Familial history, <i>n</i> (total, %)	157 (802, 19.6)
Peripheral arthritis, <i>n</i> (total, %)	391 (826, 47.1)
Hip joint involvement, <i>n</i> (total, %)	604 (817, 73.9)
JoAS, <i>n</i> (total, %)	236 (823, 28.7)
HLA-B27, <i>n</i> (total, %)	727 (767, 94.8)
TNF-blocker use, <i>n</i> (total, %)	224 (830, 26.9)
Extra-articular manifestations	
Enthesitis, <i>n</i> (total, %)	344 (805, 42.7)
Uveitis, <i>n</i> (total, %)	246 (829, 29.7)
Disease duration, mean (SD) (years)	15.1 (7.8)
Cardiac involvement, <i>n</i> (total, %)	13 (806, 1.6)
Renal involvement, <i>n</i> (total, %)	32 (806, 3.9)
Inflammatory bowel disease, <i>n</i> (total, %)	9 (806, 1.1)

Data from Kim and Kim [23]. OSKAR, Observation Study of Korean Spondyloarthritis Registry.