SPONDYLOARTHRITIS IN COLOMBIA

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"*If I have seen further than others, it is by standing upon the shoulders of giants*".

Sir Isaac Newton

Letter to Robert Hooke (15 February 1676)

To my beloved wife Sonia

To Nicolás and Valeria

To my parents

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General Introduction

INTRODUCTION

Spondyloarthritis (SpA) comprises a heterogeneous group of distinct disorders including ankylosing spondylitis (AS), non-radiographic axial SpA, psoriatic arthritis, arthritis related to inflammatory bowel disease and reactive arthritis[1]. SpA is the second most prevalent form of chronic inflammatory arthritis, with an estimated prevalence of about 0.5-1.5%[2]. This condition is characterized by inflammation as well as structural damage[3]. The inflammatory process affects the axial skeleton and the sacroiliac joints (SI), the peripheral joints and may extend to organs such as eye, skin and gut.

Clinical presentation

The disease SpA usually starts in the second or third decade of life and has a male predominance. The clinical picture includes chronic back pain, peripheral arthritis, enthesitis and extra-articular manifestations such as uveitis, psoriasis and inflammatory bowel disease (IBD)[4]. Patients present with chronic back pain and morning stiffness of the lower back, but any part of the spine can be involved. Inflammatory back pain (IBP) is typical. IBP has been clinically defined and different sets of criteria have been developed[5]. Arthritis and enthesitis are the most common peripheral manifestations that can occur at any time in the course of the disease. The joints may be swollen and/or painful and the lower limbs are most often affected, frequently in an asymmetrical fashion.

Comorbidities and risk factors

Comorbidities are frequently associated with inflammatory rheumatic diseases including SpA. In addition to the musculoskeletal manifestations for SpA and SpA-related extra-articular features, patients may also have an increased risk of cardiovascular events, arterial hypertension, metabolic syndrome, malignancies and infections[6]. An optimal detection and monitoring of comorbidities and

risk factors may have implications not only for treatment planning but also for the prevention of these conditions in daily clinical practice.

Classification criteria

As for every rheumatological disease, diagnostic criteria for SpA are lacking. Different sets of criteria have been proposed for the classification of SpA (that means: to be applied in patients with a diagnosis of SpA). According to the modified New York criteria, the presence of radiographic sacroiliitis (grade 2 bilateral or grade 3-4 unilaterally) in combination with one of the clinical criteria (low back pain or limitation of the lumbar spine or limitation of chest expansion), is mandatory in order to classify a patient as having AS[7]. The European Spondylarthropathy Study Group (ESSG)-criteria [8] and the Amor-criteria[9] were the first aiming at classifying patients along the whole disease spectrum. The entry-criterion of the ESSG criteria is the presence of IBP or peripheral arthritis. Patients with one of these entry criteria in combination with one minor criterion are classified as SpA according to the ESSG criteria. In contrast, in the Amor criteria a list of signs are included and none of them is required for classifying a patient as having SpA. In 2009 ASAS has proposed two classification criteria sets for SpA. One set can be applied in patients that have presented with predominantly axial involvement (axSpA)[10], and the other set can be applied in patients that have presented with predominantly peripheral involvement (pSpA)[11]. The axSpA-criteria can be applied in patients that have presented with chronic back pain (≥3 months) starting before the age of 45 years. This set consist of two arms: the imaging arm and the clinical arm. Patients can be classified in the imaging arm when one SpA-feature is present in addition to sacroiliitis on radiographs or magnetic resonance imaging (MRI). Patients can be classified according to the clinical arm if two SpA features are present in addition to HLA-B27 positivity. The pSpA criteria can be applied in patients that have presented with at least one of the peripheral manifestations arthritis, enthesitis

or dactylitis. A patient with peripheral manifestations can fulfil pSpA criteria if at least one of the following SpA feature is present in addition: uveitis, psoriasis, IBD, preceding infection, HLA-B27 positivity or sacroiliitis on imaging; or if at least two of the following additional SpA features are present: arthritis, enthesitis, dactylitis, IBP or a positive family history for SpA.

The ASAS/OMERACT core set

In an attempt to bring homogeneity in outcome assessment in AS, the Assessment of SpondyloArthritis international Society (ASAS) has selected a core set of variables that have been endorsed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group. This core set is intended to be used as standardised end-points in clinical trials and in clinical practice. Three scenarios for core sets have been defined: (1) disease controlling anti-rheumatic therapy (DC-ART), (2) symptom modifying anti-rheumatic drugs (SMARDs) and physical therapy and (3) clinical record keeping. The domains selected for all three core sets include 'physical function', 'pain', 'spinal mobility', 'spinal stiffness', 'fatigue' and 'patient's global assessment'. The DC-ART core sets and clinical record keeping further include 'peripheral joints/entheses' and 'acute phase reactants', and the core set for DC-ART includes 'radiographs of the spine'. Specific instruments to assess the domains for all three core set have been selected (Table).

Table ASAS/OMERACT core set for SMARD, DC-ART and specific instruments

Domains	**Instruments**
Function	BASFI
Pain	NRS/VAS (last week/spine/night/due to AS)
	NRS/VAS (last week/spine/due to AS)
Spinal mobility	Chest expansion, modified Schober, occiput to wall, cervical rotation, (lateral spinal flexion or BASMI)
Spinal stiffness	NRS/VAS (duration of morning stiffness, spine, last week)
Patient global	NRS/VAS (global disease activity last week)
Peripheral joint, entheses	Number of swollen joints (44 joint count) MASES, San Francisco or Berlin
Acute phase reactants	CRP or ESR
Radiograph spine	mSASSS on lateral lumbar spine / lateral cervical spine
Fatigue	Fatigue question BASDAI

ASAS, Assessment of SpondyloArthritis international Society; OMERACT, Outcome Measures in Rheumatology Clinical Trials; DC-ART, disease controlling anti-rheumatic therapy; SMARD, symptom modifying anti-rheumatic drugs; BASDAI, Bath Ankylosing Spondylitis Functional Index; NRS, Numerical Rating Scale; VAS, Visual Analogue Scale; BASMI, Bath Ankylosing Spondylitis Metrology Index; MASES, Maastricht Ankylosing Spondylitis Enthesis Score; CRP, C-reactive protein; ESR, Erythrocyte Sedimentation Rate; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; BASRI, Bath Ankylosing Spondylitis Radiology Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index

Clinical assessment and monitoring

Assessment and monitoring is important in systemic diseases that may present with a variety of symptoms and signs, such as SpA. Each of these symptoms can be assessed in clinical practice using different instruments. Disease monitoring should include patient history (patient oriented questionnaires), clinical parameters including spinal mobility, laboratory tests and imaging, all according to clinical presentation, as well as the ASAS core set[12]. In this regard, instruments for the assessment and monitoring of the disease have been validated for use in clinical practice as well as in clinical trials[13]. Disease activity indices are relevant for monitoring disease activity in patients with SpA. The Bath AS Disease Activity Index (BASDAI) and recently the AS Disease Activity Score (ASDAS) are the most important indices available for clinical practice. The ASDAS-CRP is recommended by ASAS and validated cut-off levels for levels of disease activity as well as improvement in disease activity have been defined[14].

Health and functioning assessment

General health and functioning are of pivotal importance when assessing the impact of the disease on the patient. Recently, the ASAS Health Index (HI) has been developed to measure functioning and health in patients with SpA aiming to better describe the impact of disease in these patients[15]. The ASAS-HI is a new and linear composite measure based on an item pool which has been developed and based on the International Classification of Functioning core set for AS. This composite index forms a unidimensional scale providing a sum score representing a wide spectrum of different levels of functioning, and it contains 17 dichotomous questions addressing the following categories: pain, emotional functions, sleep, sexual functions, mobility, self-care, community life and employment.

Magnetic Resonance Imaging and HLA-B27

In addition to the clinical picture, imaging (radiography and magnetic resonance imaging (MRI)) and laboratory data (HLA-B27 and C-reactive protein (CRP)) are important tools in daily clinical practice when assessing patients with SpA. MRI of the sacroiliac (SI) joints has become an important tool in the diagnosis and classification of SpA and its introduction as a diagnostic test has been a major advance in the field of SpA. MRI is particularly important for early diagnosis, especially because if its sensitivity to active inflammatory lesions early in the course of the disease, and often well before definite lesions on conventional radiographs are detectable[16]. This makes MRI the most sensitive imaging modality available for the detection of sacroiliitis. The role of HLA-B27 in the diagnosis, prognosis and management of SpA has been extensively investigated. HLA-B27 has been associated with an increased severity and persistence of SI-MRI- inflammation in (especially male) patients with IBP[17]. SI-MRI as well as HLA-B27 help to secure a diagnosis of axSpA and both have a

high specificity[18]. In addition to sacroiliitis on radiographs, SI-MRI as well as HLAB27 serve as entry criteria in the ASAS classification criteria for axSpA. Additionally both tests (sacroiliitis by MRI and HLA-B27 positivity) have been included in the decision tree of the original and modified Berlin diagnostic algorithm and can be applied in clinical practice[19].

Current situation regarding SpA in Colombia

Data in the literature reporting the behaviour of SpA in Colombia is limited and many efforts have been made to describe the landscape of this condition in the country. Just as in other countries in Latin America, research about SpA is far less mature than research about other rheumatic disorders such as rheumatoid arthritis (RA) and systemic lupus erythematous[20]. The research in the field of SpA performed in Colombia has been rather descriptive and based on clinical cohorts of patients in academic centers reporting disease manifestations, prognostic factors, biomarker levels and frequencies of HLA-B27.

Information from many studies performed in Colombia provide a preliminary impression with regard to clinical presentation, main features and frequency of subtypes. One of the first analyses was the characterization, description of features by subtypes and the follow-up of 139 patients with SpA[21]. Male gender, the presence of uveitis and the early age of disease onset were associated with a worse prognosis (more disease progression) of AS patients. In another study, increasing serum levels of biomarkers (IL-17, IL-23, IL-6, TNF-α, IL-1 α and CRP) were shown to be associated with poorer prognosis of patients with SpA[22]. Similarly, positive associations between enthesitis and IL-17 serum levels and between enthesitis and IL-23 synovial fluid levels were found in a small sample of 62 patients[23].

Higher frequencies of peripheral involvement have been consistently observed in Latin America. In a cohort of Colombian patients, peripheral oligo-arthritis has been reported in a range of 65% to 76% and enthesitis in a range of 67% to 86%[24]. These findings are similar to those reported in Mexico and Brazil: they found arthritis in 66% and enthesitis in 54% of the patients[25]. A rather low frequency of HLA-B27 positivity has been observed in SpA patients (about 40-45%)[26], in contrast to data reported in Europe. Differences in the prevalence of HLA-B27 in the general population, which has a wide geographic and ethnic variation (≥75% of population in Colombia is mestizo[27]), may explain these discrepancies.

Colombia faces many challenges with regard to the research in the field of SpA. The estimated total population at 2016 was more than 48 million as reported by the National Administrative Department of Statistics (DANE). The National Rheumatology Association (Asoreuma) in Colombia reports 160 rheumatologist working in 18 cities across the country especially in large cities. This means that Colombia has a rate of one rheumatologist per 302.000 inhabitants, which is three times below the optimal provision of rheumatology health-care requirements as estimated by the British Society of Rheumatology[28].

Numerically, the current workforce is insufficient to provide appropriate rheumatology care and workforce is critical in order to focus better on specific diseases such as SpA. This situation is similar to that in other countries of the continent, even though the rheumatology workforce has improved in LA during the last years[29]. Currently, five universities in Colombia provide training in rheumatology in conjunction with hospitals during a 2-years academic program.

Outline of this thesis

In general terms, the objectives of this thesis were:

1. To assess the performance of SpA classification criteria in SpA patients from Colombia and to investigate the current use of diagnostics tests in clinical practice in Colombia.

2. To investigate the prevalence of comorbidities in SpA patients in Colombia and to explore if SpA is –like other rheumatological conditions - associated with periodontitis.

3. To describe the validation and language translation of the ASAS-HI in patients with SpA in Colombia.

4. To evaluate the implementation of the ASAS/OMERACT core set for axial SpA in world-wide clinical trials.

The new ASAS classification criteria have been applied in different clinical settings especially in Europe. However, the ASAS criteria had not yet been applied and tested in a South American population. Therefore, in **chapter 2** a description of the performance of the ASAS classification criteria in a Colombian cohort of patients with SpA is presented and analysed in comparison to other criteria sets. SI-MRI and HLA-B27 are widely used in the diagnosis of axSpA and have a prominent place in the ASAS classification criteria, not only as an entry criterion but also as a related SpA feature. The relevance of both tests as central parameters in defining the spectrum of SpA as a whole (classification) is clear. However, these test are rather costly and waiting time for MRI is long in many countries, which jeopardises widespread use for diagnostic purposes in many countries among which Colombia. Many have suggested to preselect patients in the diagnostic work-up of SpA so that some unnecessary expenses for MRI/HLAB27 testing can be avoided. In **chapter 3** we investigate the patient's characteristics associated with the decision of the rheumatologist to request SI-MRI and/or HLA-B27 in clinical practice.

An increased prevalence of several comorbidities has been reported in SpA patients; the risk of developing such comorbid conditions seems to be higher in patients with SpA than in the general population. But data about such comorbid conditions in SpA patients from Latin America are scarce. In **chapter 4** comorbidities and risk factors in SpA-patients from Latin America have been investigated. A comparative analysis with the general population was performed using data from the multinational ASAS-COMOSPA study.

SpA is a condition that is characterized by inflammatory features and extra articular manifestations. Previous studies, particularly in RA, have pointed towards a relationship between periodontitis (a chronic inflammatory condition characterized by loss of the periodontal ligament and alveolar bone) and systemic rheumatic diseases[30]. But it is unclear whether SpA patients also have a higher frequency of periodontitis and data in the literature reporting a possible association is limited. Therefore, in **chapter 5** we investigate and compare the frequency of periodontitis in SpA patients with that in healthy individuals from the population.

The overall picture of impairments, limitations, and restrictions in activities or social participation of patients with SpA has been aggregated in the composite ASAS Health Index[31] This index captures the whole range of functioning and disability of patients with SpA. In order to make such an index performing properly, a thorough adaptation from English into Spanish (spoken in Colombia) is of pivotal importance. In **chapter 6** the description of the translation and cross-culturally adaptation of the English version of the ASAS-HI into Spanish-language spoken in Colombia is presented.

The ASAS/OMERACT core outcome set has importantly facilitated the development and successful regulatory approval of new treatments in AS. However, thus far the true implementation of the

core sets has not yet been evaluated. In **chapter 7** we report the results of a systematic literature review aiming at analysing and comparing the usage of domains and instruments of the core sets before vs. after the original publication of the core set in randomized clinical trials.

Chapter 8 consists of a summary and a general discussion of the findings presented in this thesis. In **chapter 9**, the summary of this thesis is provided in Dutch.

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2

Analysis and performance of various classification criteria sets in a Colombian cohort of patients with SpondyloArthritis

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ABSTRACT

Objective: To investigate the performance of classification criteria sets (ASAS, ESSG, and Amor) for spondyloarthritis (SpA) in a clinical practice cohort in Colombia, and provide insight into how rheumatologists follow the diagnostic path in patients suspected of SpA.

Methods: Patients with a rheumatologist's diagnosis of SpA were retrospectively classified according to three criteria sets. Classification rate was defined as the proportion of patients fulfilling a particular criterion. Characteristics of patients fulfilling and not fulfilling each criteria were compared.

Results: The ASAS criteria classified 81% of all patients (n=581) as having either axial-SpA (44%) or peripheral-SpA (37%), whereas a lower proportion met ESSG-criteria (74%) and Amor-criteria (53%). There was a high degree of overlap among the different criteria, and 42% of the patients met all three criteria. Patients fulfilling all three criteria sets were older (36 vs. 30 years), had more SpA-features (3 vs. 1 features) and more frequently had a current or past history of back pain (77% vs. 43%), inflammatory back pain (47% vs. 13%), enthesitis (67% vs. 26%) and buttock pain (37% vs. 13%) vs those not fulfilling any criteria. HLA-B27, radiographs and MRI-SI were performed in 77%, 59% and 24% of the patients respectively.

Conclusion: The ASAS criteria classified more patients as having SpA in this Colombian cohort when the rheumatologist's diagnosis is used as an external standard. Although physicians do not perform HLA-B27 or imaging in all patients, they do require these tests if the clinical symptoms fall short of confirming SpA and suspicion remains.

INTRODUCTION

Spondyloarthritis (SpA) comprises a heterogeneous group of diseases that share common clinical, radiological and genetic characteristics. SpA includes among others ankylosing spondylitis (AS), undifferentiated SpA (uSpA), reactive arthritis (ReA), psoriatic arthritis (PsA) and SpA associated with inflammatory bowel disease (IBD) [1]. Several sets of classification criteria have been developed for clinical and epidemiological studies. The European Spondylarthropathy Study Group (ESSG) [2] and the Amor [3] were the first criteria aimed at classifying patients along the whole disease spectrum. However, these two criteria sets do not perform as well in early recognition of the disease [4 5] and do not distinguish between axial and peripheral disease in separate sets[6]. Recently, the Assessment of SpondyloArthritis international Society (ASAS) criteria were developed for the classification of patients with SpA and for better distinguishing between patients with axial-SpA (axSpA) [7] and peripheral-SpA (pSpA) [8].

Diagnostic criteria for SpA are lacking but diagnostic algorithms have been developed. The adaptation of the 'Berlin algorithm', might be a useful tool in clinical practice [9]. In clinical setting, a flexible approach is often applied: complete clinical data are rarely obtained, important clinical questions could be missed, and the rheumatologist, rather than a fixed protocol, determines whether additional clinical testing (imaging, HLA-B27) is necessary. Consequently, applying classification criteria including such "on request only" tests may suffer from many missing data and yield different results in clinical practice than in validation cohorts.

The ASAS-SpA criteria [6,7] were recently applied in different clinical settings. The full criteria were tested in a cohort with long-standing SpA [10], and the pSpA criteria were tested in a particular cohort of patients with recent-onset arthritis [11], both European cohorts. However, to our knowledge the

ASAS-criteria have not been applied in a South-American population. By default, classification criteria in clinical practice should be applied to patients that have been diagnosed by the rheumatologist; they are not diagnostic criteria. Consequently, they should be tested against the clinical judgment of the rheumatologist. Because of the nature of classification criteria, it can be expected that sensitivity is relatively low, but if performing well, specificity should be high [5].

The main objectives of this study are twofold: first, to test how the ASAS-criteria perform in the context of the clinical Colombian rheumatology setting in comparison to other criteria sets. Second, to provide a general insight about how rheumatologists follow the diagnostic path in a patient suspected of having SpA. The cohort was established before the development and implementation of ASAS-criteria; therefore, the participating rheumatologists were unlikely to be biased with respect to the application of these criteria.

METHODS

Patients

Consecutive patients were included between January-2002 and June-2010 in a single-centre study of patients referred to a specialised rheumatology outpatient clinic in a national referral centre. Patients with a clinical diagnosis of SpA (defined as the "reference standard") by one of two rheumatologists who were considered experts in the field (RV and JL), were selected and included in the study on the first visit to the clinic. The inclusion of the patients was based on the clinical diagnosis and not on any set of classification criteria. Then, this cohort of patients based on SpA clinical diagnoses by the rheumatologist, was further analysed for the characteristics included in the ASAS, ESSG and Amor-criteria. Patient information was based on the information from the clinical record. The institutional ethics committee approved this study, which was conducted under

the principles of Helsinki declaration. Patients signed informed consent to collect, file and use the data.

Demographic, clinical and imaging characteristics

The following information was included in the database: patient demographics, spinal mobility measures (occiput to wall distance, chest expansion, modified Schober test, lateral spinal flexion), laboratory tests [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and HLA-B27 testing]; age at assessment, age at first symptoms, symptom duration, family history of SpA and the history (past) and presence (current) of chronic back pain (more than 3 months), inflammatory back pain, alternating buttock pain, asymmetric oligoarthritis (predominantly in lower limbs), enthesitis (heel pain), dactylitis ("sausage-shape" digit), uveitis (confirmed by ophthalmologist) and psoriasis. Functional capacity and disease activity were measured by the BASFI [12] and BASDAI[13], respectively. The Ankylosing Spondylitis Disease Activity Score (ASDAS), was also calculated: ASDAS-ESR and ASDAS-CRP[14]. Acute phase reactants, HLA-B27, and the results of plain radiographs and MRI of sacroiliac joints (SI) were retrieved from the clinical file, as requested by rheumatologist. All data was collected at the initial visit to the clinic. Data related to follow-up were not included.

The rheumatologist interpreted the radiographs according to the modified New York classification for radiographic sacroiliitis [15]. Sacroiliitis on MRI was defined according to the local experienced musculoskeletal radiologist's interpretation of the presence of active inflammatory changes in the SI-joint [16]. This is according usual clinical practice (no central reading was done). The rheumatologists assessed the patients in the clinic and provided the clinical diagnosis of SpA categorized by subtypes: AS, uSpA, ReA, PsA and IBD. It was recorded in the clinical file and used as the external standard to test against.

Criteria for classification

Retrospectively each patient who had a clinical diagnosis of SpA was classified according to ASAS axial and peripheral SpA, ESSG and Amor-criteria. If the presenting symptom was 'back pain', patients were classified according to the axSpA-criteria. If the presenting symptom was 'arthritis, enthesitis and/or dactylitis', patients were classified according to the pSpA-criteria (also if they reported back pain in the past). The ESSG and Amor-criteria were applied using radiographs for the imaging criterion. In these criteria (ESSG and Amor), when the patient had MRI findings of "sacroiliitis on MRI" (active inflammatory changes), this finding was used as a substitute for radiographic damage into the original criteria to fulfill the imaging criterion. If information on a SpA feature or a test was not available, it was considered absent.

Data analyses

Disease characteristics were analysed using descriptive statistics, such as mean (SD) for continuous variables and percentages for categorical variables. The classification rate was defined as the proportion of patients fulfilling a particular criterion (numerator) and the total number of patients in the cohort (denominator). The concordance between the different criteria sets was analysed representing the proportion of patients who were also captured by another criterion. Venn-diagrams were constructed representing patients who met one or more of the ASAS, ESSG, and Amor-criteria sets. In addition, we present patients with overlap between clinical diagnosis and fulfillment in the axial and peripheral ASAS-criteria in a Venn-diagram. Disease characteristics of patients fulfilling each classification criteria set vs. those who did not, were compared by t-test for continuous variables and by Chi-Square test for categorical variables. All analyses were performed using SPSS version 20, p-values ≤0.05 were considered statistically significant.

RESULTS

Patient's characteristics

The population consisted of 581 patients. Table-1 presents the descriptive characteristics of the cohort in total and split by disease subtype, according to clinical diagnosis (external standard). Overall, 72% of patients were men with mean (SD) age of 35 (13.5) years, symptom duration of 7.3 (9.7) years and age at the beginning of the symptoms of 28 (10.3) years. In total, 76% of patients had a history of -or had current- chronic back pain, and 64% of these had IBP. Seventy-two percent had a history of -or had current- asymmetric oligo-arthritis, and 57% had a history of -or had current- enthesitis. Disease activity was calculated separately for patients with axial or peripheral SpA. Axial-SpA patients had a mean (SD) BASDAI of 5.4 (2.4) an ASDAS-CRP of 2.6 (0.8) and an ASDAS-ESR of 3.0 (0.9). Peripheral-SpA patients had a BASDAI of 5.3 (2.5), an ASDAS-CRP of 2.3 (0.9) and an ASDAS-ESR of 3.0 (0.9).

Table 1. Descriptive characteristics of the patients according to the rheumatologist's clinical SpA diagnosis.

Characteristic	Total n=581	AS n=169 (29.1)	uSpA n=230 (39.6)	ReA n=156 (26.9)	PsA n=21 (3.6)	IBD n=5 (0.9)
Male gender, N (%)	417 (71.7)	117 (69.2)	161 (70)	126 (80.1)	12 (57.1)	1 (20)
Age, (years)	35±13.5	39.2±14.2	34.8±12.7	27.4±9.7	48.3±10.7	49.1±15.7
Age at first symptom (years)	28±10.6	28.9±11.3	28.4±10.1	24.5±8.2	35.8±14.9	43.1±18.6
Symptom duration (years)	7.3±9.7	10.4±11.1	6.6±8.9	3.4±6.7	12.5±12.7	6.0±8.0
Chronic back pain, * N (%)	439 (75.6)	169 (100)	195 (84.8)	58 (37.2)	13 (61.9)	4 (80)
IBP, * N (%)	258 (44.4)	111 (66.7)	111 (48.3)	29 (18.6)	5 (23.8)	2 (40)
Buttock pain, * N (%)	172 (29.6)	71 (42)	68 (29.6)	27 (17.3)	4 (19)	2 (40)
Asymmetric oligoarthritis, * N (%)	419 (72.1)	106 (62.7)	143 (62.2)	148 (94.9)	18 (85.7)	4 (80)
Enthesitis, * N (%)	332 (57.1)	118 (69.8)	138 (60)	65 (41.7)	10 (47.6)	1 (20)
Dactyilitis, * N (%)	84 (14.4)	30 (17.8)	23 (10)	25 (16)	4 (19)	2 (40)
Pos family history, N (%)	31 (5.3)	13 (7.7)	8 (3.5)	9 (5.8)	1 (4.8)	0 (0)
Uveitis, * N (%)	35 (6)	16 (9.5)	13 (5.7)	5 (3.2)	0 (0)	1 (20)
Psoriasis, * N (%)	27 (4.6)	5 (2.9)	2 (0.8)	0 (0)	20 (95.2)	0 (0)
IBD, * N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (100)
Preceding infection, N (%)	210 (36.1)	32 (18.9)	32 (13.9)	144 (92.3)	2 (9.5)	0 (0)
HLA-B27 positive, N (%)	194 (43.9) n=441	84 (62.7) n=134	56 (31.3) n=179	52 (46.4) n=112	1 (8.3) n=12	1 (25) n=4
CRP (mg/dl)	11.7±34.8 n=178	5.9±12.2 n=39	8.7±31.7 n=82	21.7±49.1 n=51	5.6±4.9 n=4	5.1±6.8 n=2
ESR (mm/hr)	25.1±17.7 n=302	21±13.4 n=57	20.6±15.7 n=125	32.3±19.6 n=112	22.6±15.3 n=6	36±0 n=2
Sacroiliitis X-ray, N (%)	158 (45.8) n=345	154 (98.7) n=156	0 (0) n=117	0 (0) n=60	2 (22.2) n=9	2 (66.7) n=3
Sacroiliitis MRI, N (%)	69 (50.3) n=137	34 (77.3) n=44	33 (47.1) n=70	0 (0) n=20	1 (50) n=2	1 (100) n=1

Values are given as the means (SD) for the continuous variables and as a percentage for the categorical variables, unless otherwise specified.
* refers to a history (past) or the presence (current) of these features at the time of assessment
AS, ankylosing spondylitis; uSpA, undifferentiated spondyloarthritis; ReA, reactive arthritis; PsA, psoriatic arthritis; IBD, SpA associated with inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; IBP, inflammatory back pain; ASDAS, Ankylosing Spondylitis Disease Activity Score.

Imaging and lab characteristics

HLA-B27 testing was performed in 77% of the patients and 43.9% of them were positive. Regarding imaging, radiographs and MRI-SI were performed in 59% and 24% of the patients respectively. Splitting by disease subtype, the subgroup of patients in which most information was available was the subgroup of AS: radiographs: 92%; MRI: 26%; and HLA-B27: 80%. The subgroup in which least data were available was the subgroup of ReA: radiographs: 38%; MRI: 13%; and HLA-B27: 71%. In the subgroup of patients with chronic back pain (past history or current), radiographs were required as complementary testing in the majority of these patients (85%) and less frequently MRI-SI (28%). Patients with back pain in which imaging was performed, sacroiliitis on radiographs was detected in 54%, and MRI-SI inflammation in 56%. HLA-B27 testing was performed in 80.1% of these patients, and 43.6% of them were positive.

Performance of classification criteria

In total, 538 of the 581 patients (93%) in the cohort met at least one criteria set: ASAS: 81% (43.4% had axSpA, and 37.2% had pSpA); ESSG: 74%; Amor: 53%; and 69% (n=399) of patients met two criteria sets. When MRI was used as a substitute for radiographic sacroiliitis, the classification rate slightly increased to 75% for ESSG and to 58% for Amor. The performance of each criteria set is summarized in table-2. All patients with a diagnosis of AS by the rheumatologist fulfilled at least one of these three criteria sets, and 56% of these patients fulfilled all three criteria sets. In particular, patients with a clinical diagnosis of ReA (40%) and uSpA (35%) often fulfilled all three criteria sets, which may reflect the degree of overlap in the criteria for those disease subtypes. Evaluating the ESSG and Amor-criteria, the addition of MRI instead of radiographs to the criteria set did not substantially modify the level of concordance with the ASAS-criteria, which increased from 71.3% to 72.5% and from 57.1% to 60.9% respectively (table-3).

Table 2. Number and proportion of patients meeting the different criteria sets. The classification rate was defined as the proportion of patients fulfilling a particular classification criteria set.

Criteria set	N=581	(%)	CI (95%)
ASAS SpA criteria	468	80.6	77.1 – 84.7
ASAS axial SpA	252	43.4	39.3 – 47.5
Imaging arm	198	34.1	
Clinical arm	54	9.3	
ASAS peripheral SpA	216	37.2	33.2 – 41.3
ESSG criteria	431	74.1	70.4 - 77.7
ESSG with MRI pos included*	438	75.4	71.7 – 78.9
Amor criteria	309	53.1	49.0 – 57.3
Amor with MRI pos included*	335	57.7	53.5 – 61.7

*Inclusion of MRI as a surrogate for radiographic damage of sacroiliitis (active inflammatory changes) into the original criteria. ESSG, European Spondylarthropathy Study Group; ASAS, Assessment of Spondyloarthritis international Society; MRI, magnetic resonance imaging.

Table 3. Concordance among the different classification criteria sets.

Criteria	ASAS SpA	ESSG	ESSG +MRI	Amor
ESSG	71.3	-	-	-
ESSG + MRI*	72.5	98.5	-	-
Amor	57.1	70.4	69.2	-
Amor + MRI*	60.9	72.2	72.6	95.5

*Inclusion of MRI as a surrogate for radiographic damage of sacroiliitis (active inflammatory changes) into the original criteria. ESSG, European Spondylarthropathy Study Group; ASAS, Assessment of Spondyloarthritis international Society; MRI, magnetic resonance imaging.

No single SpA feature explained differences in the fulfilment of classification criteria. Chronic back pain, IBP, enthesitis and alternating buttock pain were significantly more common in those patients meeting all three criteria sets compared with those who did not meet any of the criteria, nevertheless these features were frequently present in both groups (table-4). Interestingly, in the group of patients who fulfilled ESSG or Amor but not the ASAS-criteria, HLA-B27 positivity was

remarkably lower (4.5%) than in those who did not fulfil ASAS and ESSG-criteria (46%) or ASAS and Amor-criteria (41%). Additionally, CRP values were higher in the group of patients who did not fulfil any of the criteria compared with those who fulfilled all criteria.

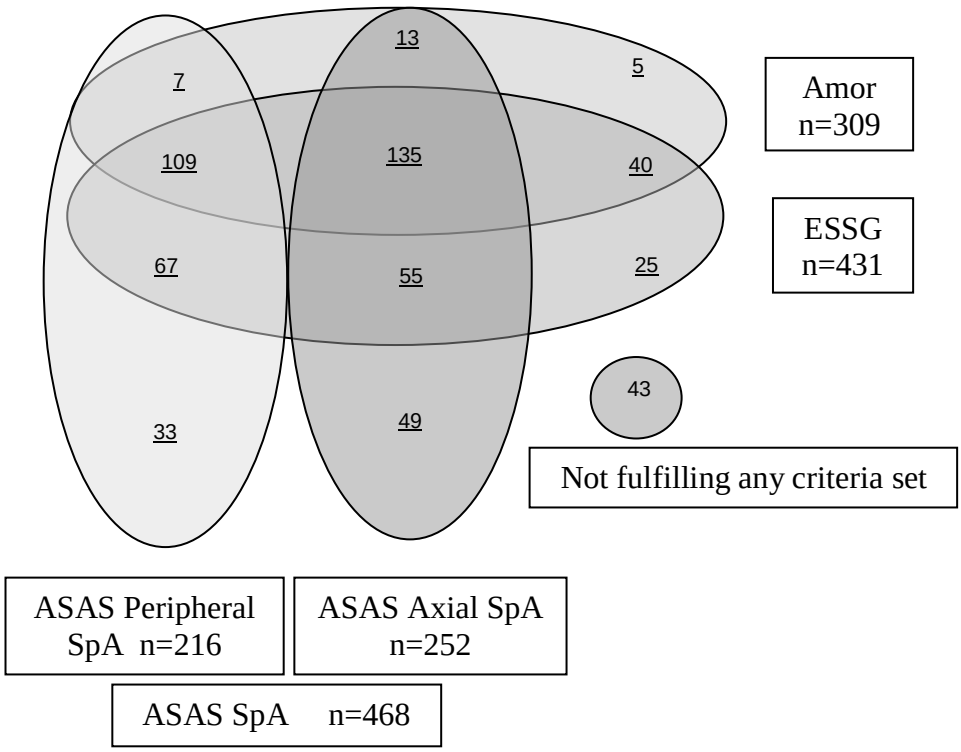
The overlap in criteria fulfillment (figure-1) was presented using a Venn-diagram representing the numbers of patients with any clinical diagnosis of SpA fulfilling each criteria set. A substantial percentage of patients (42%, n=244) met ASAS and ESSG as well Amor-criteria. In contrast, relevant numbers of patients with a clinical diagnosis of SpA fulfilled one classification criteria set exclusively: Only ASAS-axSpA: 49 patients; only ASAS-pSpA: 33 patients; only ESSG: 25 patients; and only Amor-criteria: 5 patients.

Table 4. Comparison of the characteristics of patients fulfilling (+) and not fulfilling (-) each criteria set.

	ASAS SpA			ESSG			Amor		
Characteristic	**(+)**	**(-)**	**p**	**(+)**	**(-)**	**p**	**(+)**	**(-)**	**p**
Male gender, N (%)	343 (73.3)	74 (65.5)	0.098	297 (68.9)	120 (80)	**<0.001**	208 (67.3)	209 (76.8)	**0.011**
Age, (years)	35.4±13.7	33.5±12.8	0.256	35.8±13.5	32.5±13.4	**0.030**	36.1±13.3	33.6±13.7	0.051
Age at first symptom (years)	28±10.9	27.9±9.2	0.887	28.3±10.7	26.9±10.4	0.220	28.8±11.1	26.8±9.8	0.051
Symptom duration (years)	7.6±9.9	6.0±8.9	0.188	7.6±9.8	6.4±9.3	0.319	7.5±9.3	7.1±10.4	0.653
Chronic back pain, N (%)	369 (78.9)	70 (62)	**<0.001**	335 (77.7)	104 (69.3)	**0.039**	254 (82.2)	185 (68)	**<0.001**
IBP, N (%)	227 (48.5)	31 (27.4)	**<0.001**	202 (46.9)	56 (37.3)	**0.043**	141 (45.6)	117 (43)	0.527
Buttock pain, N (%)	146 (31.2)	26 (23)	0.087	144 (33.4)	28 (18.7)	**<0.001**	112 (36.3)	60 (22.1)	**<0.001**
Asymmetric oligoarthritis, N (%)	353 (75.2)	67 (59.3)	**<0.001**	306 (71.0)	113 (75.3)	0.308	222 (71.8)	197 (72.4)	0.876
Enthesitis, N (%)	287 (61.3)	45 (39.8)	**<0.001**	266 (61.7)	66 (44)	**<0.001**	211 (68.3)	121 (44.5)	**<0.001**
Dactylitis, N (%)	76 (16.2)	8 (7.1)	0.013	68 (15.8)	16 (10.7)	0.125	55 (17.8)	29 (10.7)	0.015
Pos family history, N (%)	28 (6)	3 (2.7)	0.158	27 (6.3)	4 (2.7)	0.091	20 (6.5)	11 (4)	0.194
Preceding Infection, N (%)	175 (37.4)	35 (31)	0.202	149 (34.6)	61 (40.7)	0.181	104 (33.7)	106 (39)	0.183
Uveitis, N (%)	31 (6.6)	4 (3.5)	0.216	25 (5.8)	10 (6.7)	0.701	24 (7.8)	11 (4)	0.060
Psoriasis, N (%)	9 (1.9)	18 (15.9)	0.281	16 (3.7)	11 (7.3)	0.07	13 (4.2)	14 (5.1)	0.591
IBD, N (%)	3 (0.6)	2 (1.7)	0.451	5 (1.1)	0 (0)	0.185	4 (1.2)	1 (0.3)	0.227
HLA-B27 positive, N (%)	191 (51.3)	3 (4.5)	**<0.001**	143 (43.3)	51 (46)	0.631	112 (46.3)	82 (41.2)	0.285
CRP (mg/dl)	10.4±34.9	16.5±34.8	0.342	9.2±2.7	19.1±6.6	0.100	9.4±3.6	14.3±3.8	0.345
ESR (mm/hr)	25.9±17.5	22.4±18.2	0.159	24.4±17.2	27±19	0.256	22.7±16	27.3±18.9	**0.025**
Sacroiliitis X-ray, N (%)	158 (53.7)	0 (0)	-	121 (46)	37 (45.1)	0.888	97 (50)	61 (40.4)	0.076
Sacroiliitis MRI, N (%)	69 (58.5)	0 (0)	-	54 (50)	15 (51.7)	0.869	37 (50.7)	32 (50)	0.936

Continuous variables were compared by t-test and categorical variables were compared by Chi-square test Values are given as the means (SD) for the continuous variables as a percentages for the categorical variables, unless otherwise specified.
AS, ankylosing spondylitis; uSpA, undifferentiated spondyloarthritis; ReA, reactive arthritis; PsA, psoriatic arthritis; IBD, SpA associated with inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; IBP, inflammatory back pain; ASDAS, Ankylosing Spondylitis Disease Activity Score.

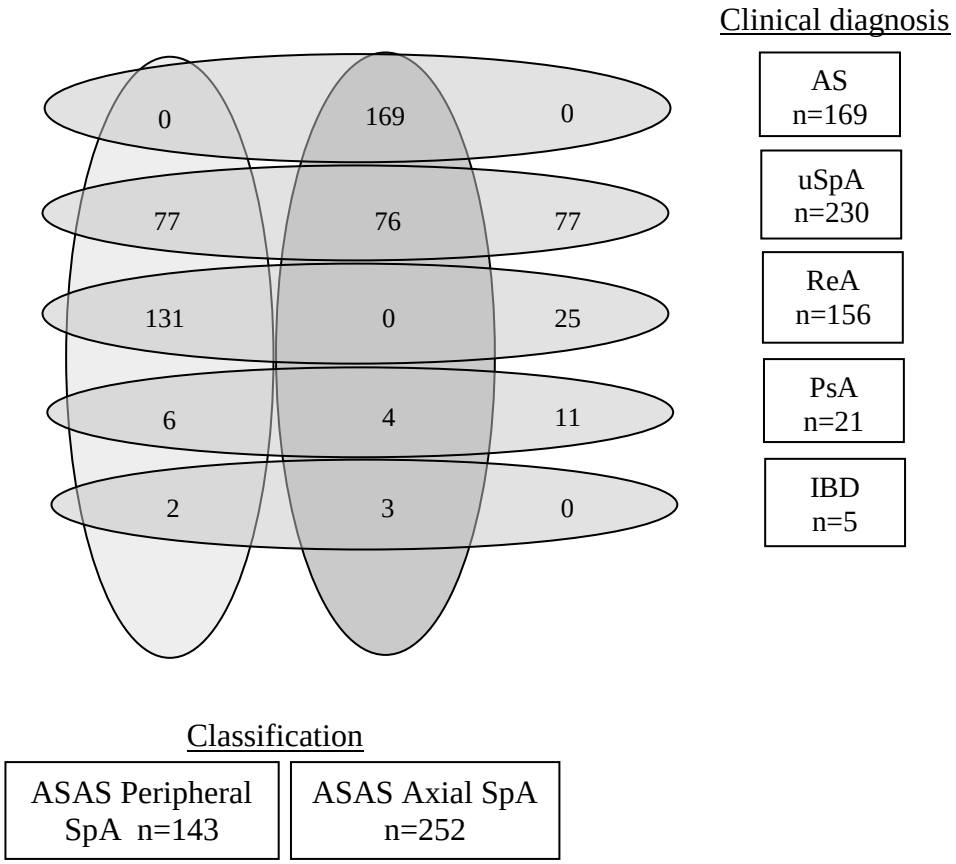
Figure 1. Number of patients meeting the original classification criteria for spondyloarthritis and the overlap of these criteria sets (n=581).



ESSG, European Spondylarthropathy Study Group; ASAS, Assessment of Spondyloarthritis international Society.

Most important, however, is to investigate how ASAS-criteria fulfillment relates to clinical diagnosis. This analysis is visualized in the Venn-diagram in Figure-2: All patients with a clinical diagnosis of AS fulfilled the axSpA-criteria, and all patients with a clinical diagnosis of ReA fulfilled pSpA-criteria. The other subcategories of clinical diagnoses, however, were either captured by axSpA-criteria or by pSpA-criteria, and frequently, a clinical diagnosis of SpA could not be confirmed by axSpA or pSpA-criteria.

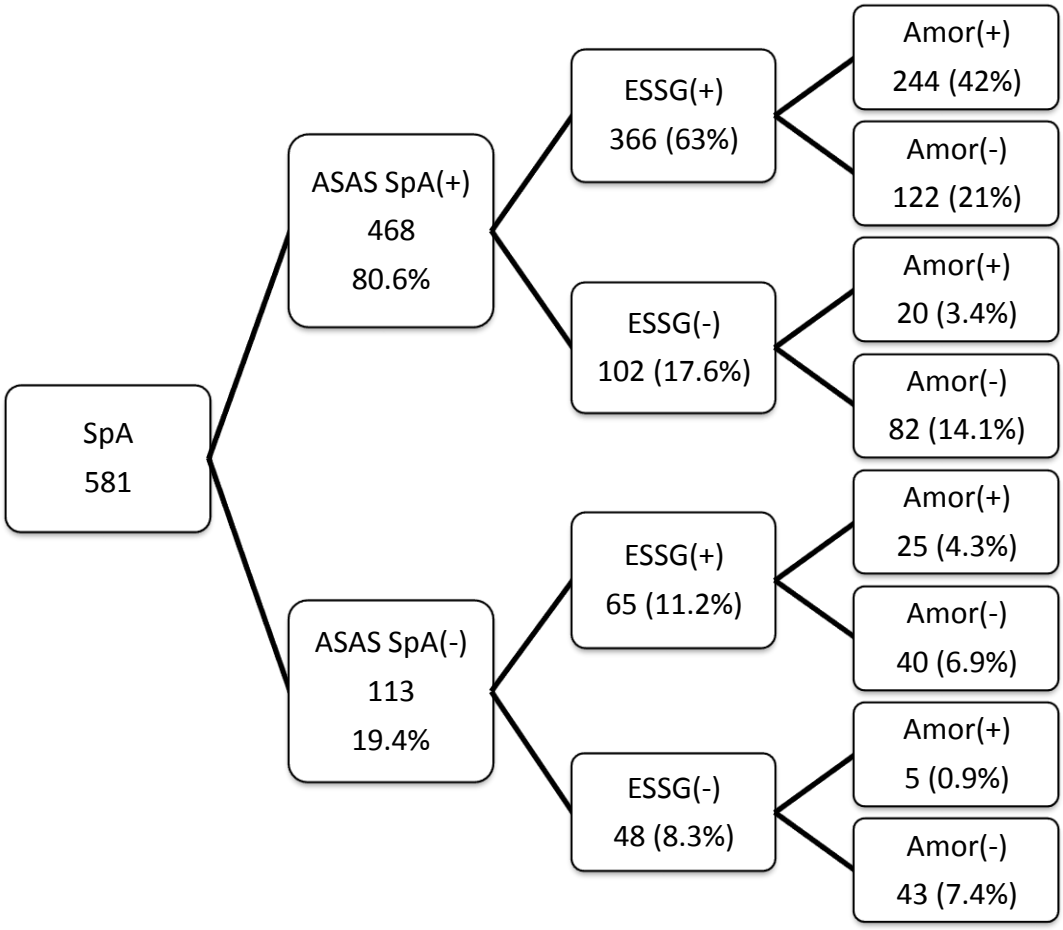
Figure 2. Number of patients meeting the ASAS classification criteria according to clinical diagnosis made by rheumatologist.



ASAS, Assessment of Spondyloarthritis international Society; AS, ankylosing spondylitis; uSpA, undifferentiated SpA; ReA, reactive arthritis; PsA, psoriatic arthritis; IBD, SpA associated with inflammatory bowel disease.

Figure-3 and Table-3 describe criteria overlap in two manners: Table-3 describes the concordance rates between ASAS, ESSG and Amor, as well as these rates with MRI-modified ESSG and Amor-criteria. Concordance between ASAS and ESSG is approximately 70% and between ASAS and Amor approximately 60%. Of note, the concordance rates did not increase significantly by substituting the radiologic criterion by the MRI criterion. Figure-3 starts with a clinical diagnosis of SpA. The large majority of patients with a clinical diagnosis fulfill any of the existing criteria, but there is marked heterogeneity in doing so: all combinations of criteria can be found, and there is only a small fraction of patients that classifies consistently negative.

Figure 3. Cumulative effect of the classification rate according to the proportion of patients who fulfill (+) and those who did not fulfil (-) the original criteria in all patients with a clinical diagnosis of SpA (n=581).



DISCUSSION

This study has shown that the ASAS-criteria are most sensitive in classifying patients as having SpA, using the rheumatologist's clinical diagnosis as an external standard. The ASAS-criteria were more sensitive than the ESSG and Amor, even if these latter were supplied with information about sacroiliitis on MRI as a SpA feature. The addition of MRI, however, did not substantially increase the classification rate of the ESSG and Amor and did not importantly influence the concordance rate with the ASAS-criteria.

A moderately high degree of concordance (50-70%) was observed among the different criteria sets using the clinical diagnosis as the external reference, adding to the credibility of the concept that these criteria classify a considerable proportion of patients with similar and rather homogeneous characteristics. While none of the single SpA feature was particularly important in explaining differences in the fulfilment of several sets of classification criteria, chronic back pain, IBP, enthesitis and alternating buttock pain were the parameters that particularly differed between patients with a clinical diagnosis of SpA fulfilling and those not fulfilling the criteria. This means that Colombian physicians in this clinic tend to consider a diagnosis of SpA if patients present with these characteristics. These features were remarkably similar across all criteria, which suggests that they are among the core characteristics of SpA, which is entirely in line with the 'Gestalt' -the 'picture'- of this disease.

The results of this study allow interesting interpretations about how rheumatologists in this clinic in Colombia make a clinical diagnosis of SpA. The rate of HLA-B27 positivity in the group of patients with a clinical diagnosis of SpA who did not fulfill the ASAS-SpA criteria was low, and was lower than in those patients with a clinical diagnosis of SpA not fulfilling other criteria sets for SpA. This low rate of HLA-B27 in those patients contrasts with the prominent role of HLA-B27 as the entry criterion in the clinical arm of axSpA-criteria, and as a SpA feature in both axial and peripheral ASAS SpA-criteria. Apparently, rheumatologists did not pay too much attention to the presence or absence of HLA-B27 when considering a clinical diagnosis of SpA, which is in line with the widely disseminated message in the past that many healthy individuals may be HLA-B27 positive without having AS [17]. Furthermore, patients who did not fulfil any of the criteria sets, had a higher CRP level than patients who fulfilled at least one the criteria sets. Apparently, the rheumatologist still diagnosed them as having SpA. It seems that a clinical diagnosis of SpA is more easily made when

signs of inflammation are present, even though characteristic features of SpA may be lacking or insufficiently present.

AS as a clinical diagnosis implied the fulfillment of more criteria sets. Patients with AS had the highest availability of important tests (imaging and HLA-B27), as compared with other subtypes. Apparently, physicians who suspect a patient of having AS often test not only HLA-B27 but also ask for MRI, even though both a HLA-B27 and an MRI result are formally redundant. This finding regarding additional testing was similar when analyzing patients who had chronic back pain. Interestingly, these tests were far less frequently ordered if a patient had ReA or uSpA, while in the context of current thinking, they would have been most useful to corroborate a clinically made diagnosis. Explanations could be that in case of a patient with 'clinical AS' the physician wants to have supportive information, for example because the pelvic radiograph is often equivocal [18], which may lead to the fulfillment of more criteria sets. In case of ReA, on the other hand, the physician may not consider the disease as part of the (axial) SpA-spectrum and does not require supportive tests, which will lead to the fulfillment of less criteria sets. In support of this thesis, we could delineate a considerable number of patients with a clinical diagnosis of SpA who fulfilled only one set of classification criteria: these patients often had a diagnosis of uSpA or ReA.

Our results are in concordance with other studies reporting on the validity of the ASAS-criteria in a clinical rheumatology setting using the clinical diagnosis as reference standard. The DECLIC-study [19] performed in patients with chronic back pain, the SPACE-cohort [20], which is a cohort of patients younger than 45 years with chronic back pain lasting between 3 months and 2 years, and the Spanish ESPERANZA-program [21], which includes patients referred to clinics for early SpA, all found that the ASAS-criteria had a higher sensitivity when tested against a clinical diagnosis of axSpA than

the ESSG or Amor-criteria. In contrast, in the DESIR[22] cohort (patients with recent onset of inflammatory back pain) a higher sensitivity was found for the Amor and ESSG criteria (79 and 78%) as compared to ASAS criteria (70%).

The results of this study are also in line with previous Latin-American studies reporting a higher presence of peripheral manifestations in SpA (Latin-America [23] and Colombia [24,25,26]). The high frequency of arthritis (72%) and enthesitis (57%) in our study are also in concordance with findings in Mexican mestizo [27] patients (peripheral arthritis in 66% and enthesitis in 47%) that had predominant involvement of lower limbs. Brazilian SpA-patients reported entheseal involvement in 54% [28]. Similarly, in a study comparing the clinical expression of patients with AS between Latin-America and Europe [29] a higher frequency of peripheral arthritis (57% vs 42%) and enthesitis (54% vs 38%) was found in Latin-America. The GESPIC-Cohort [30] only reported peripheral arthritis being present in 14% of the AS patients and in 18% of the in non-radiographic axSpA. Similar findings were reported for enthesitis.

The frequency of HLA-B27 in our cohort was also rather low, not only in AS (63%) but also in SpA in general (44%), as compared to the frequency of HLA-B27 in AS patients in Europe and North America (80-90%) [31]. This rather low frequency was similar to other studies in Latin America [32] and was similar to data recently reported in a Colombian study analyzing HLA-alleles[33], finding a frequency of HLA-B27 of 40% in SpA patients. This may be explained by differences in the prevalence of HLA-B27 in the general population, which has a wide ethnic and geographic variation. However, studies assessing the frequency of HLA-B27 in Colombian patients with AS are lacking.

There is an important problem regarding the interpretation of the performance of criteria in observational studies like ours. In some observational studies, such as SPACE and DESIR, MRI and HLA-B27 testing are performed in all patients 'by protocol', regardless of the likelihood of a diagnosis of SpA. In other observational SpA cohorts, including the Colombian cohort, many of these tests are performed on clinical indication only, namely in those patients with the highest probability of having SpA, or –alternatively- in those in whom the presence of other SpA-features does not convince the diagnosing physician. Here the danger of bias by indication arises, because the presence of a certain test result may reflect the perceived severity of the disease, and consequently information about these tests in patients with milder symptoms may be lacking. Additionally, the lack of information about HLA-B27 and MRI in a proportion of patients could have influenced the performance of the classification criteria, since these parameters (HLA-B27 and MRI) have a rather prominent place in the classification criteria (HLA-B27 in the Amor criteria and HLA-B27 and MRI in the ASAS classification criteria). It is unclear how this lack of data may have impacted the results.

There are several limitations in this study, including the retrospective design and missing data, which reflects the daily clinical practice. First, there was not a fixed protocol requesting for additional clinical testing for the totality of patients; in contrast, these test were performed based on the opinion of the physician. Second, we selected the rheumatologist diagnosis of SpA as the external standard. A concern with our choice of external standard is that the rheumatologist´s diagnosis might be biased and influenced by current knowledge, by the experience and the existing criteria classification sets, by new diagnostics developments (MRI) or by discussion with experts. Third, data were only collected at the initial visit to the clinic (cross-sectional approach) and there was no information of follow-up visits available, not information about (response to) treatment.

The strength of this study is that the data were collected before the establishment of the ASAS-criteria. The clinical diagnosis in many rheumatic conditions such as SpA is made based on a combination of suggestive symptoms, physical examination findings and complementary testing; therefore, it is guided largely by the “gestalt” rather than quantitative items. These factors could indeed influence the clinical diagnosis and therefore the request of additional testing. On the other hand, this is what is happening in clinical practice to define prognosis and start treatment.

In conclusion, compared with the ESSG and Amor, the ASAS-criteria classify more patients as having axial or peripheral SpA when the rheumatologist’s diagnosis is used as an external standard. Although Colombian physicians in this clinic do not perform HLA-B27 testing or imaging in all patients suspected of having SpA, they do require these tests if the clinical symptoms fall short and suspicion remains.

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3

Factors associated with the decision of the rheumatologist to order sacro-iliac joints magnetic resonance imaging (SI-MRI) or HLA-B27 testing in the diagnostic work-up of patients with spondyloarthritis in clinical practice

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ABSTRACT

Objective To evaluate the patients' characteristics associated with the clinical decision to request SI-MRI and/or HLA-B27 in patients with SpA in daily practice.

Methods Patients referred to a rheumatology outpatient-clinic in a national referral-centre were selected. Patients with a clinical diagnosis of SpA according to the rheumatologist were included. SI-MRI and HLA-B27 was available for patients in whom the rheumatologists had ordered these tests. Characteristics associated with ordering SI-MRI or HLA-B27 were identified with univariable analyses. Variables with p-value <0.05 and > 80% completeness were selected for further analysis. A multivariable logistic regression analysis was used to evaluate the determinants related with the decision to perform SI-MRI and/or HLA-B27 and odds ratios with 95% confidence intervals were calculated.

Results In total, 581 patients with SpA were included in the cohort, 72% were men, mean age 34.6±12.1 and disease duration 7.3±9.7 years. Of these patients, 24% (n=137) had SI-MRI and 77% (n=441) had HLA-B27 tests ordered. Independently predictive factors for ordering a SI-MRI were the presence of IBP (OR=1.81), enthesitis (OR=1.57) and the number of initial-symptoms at presentation (OR=1.27 per additional symptom present). Independently predictive factors of HLA-B27 testing were the number of initial-symptoms (OR=1.45 per symptom) and uveitis (OR=3.19).

Conclusions. This study strongly suggests that rheumatologists use certain clinical clues to decide if they order expensive and scarce tests in the diagnostic work-up of SpA patients. These manifestations may increase the efficiency of these tests in clinical practice and suggest that clinical reasoning follows principles of Bayesian theory.

INTRODUCTION

Spondyloarthritis (SpA) comprises a heterogeneous group of related diseases that are genetically linked and share characteristic clinical features associated with the inflammation of sacroiliac joints and the presence of HLA-B27 [1]. Clinically, SpA patients may present with axial and peripheral joint manifestations, entheseal involvement, and extra-articular features, such as uveitis and psoriasis [2]. In addition to clinical findings, imaging [radiography and sacroiliac joint magnetic resonance imaging (SI-MRI)] [3] and laboratory data [HLA-B27 and C-reactive protein (CRP)] [4] are important diagnostic tools in clinical practice.

In the last two decades, MRI has been increasingly used to assess patients with clinically suspected SpA [5]. Currently, MRI has become an important tool in SpA and its introduction as a diagnostic test for SpA has been a major advance [6], mainly because active inflammatory lesions are visible on MRI long before definite lesions on conventional radiographs are detectable [7]. It makes MRI the most sensitive imaging modality available for the detection of sacroiliitis.

Since the role of HLA-B27 as a marker of AS has first been reported in 1973, its potential role in the diagnosis, prognosis and management of SpA has been extensively investigated. HLA-B27 is known to be associated with earlier age at disease onset in ankylosing spondylitis (AS) [8], increased severity and persistence of SI-MRI- inflammation in patients with inflammatory back pain (IBP) [9] and with a higher likelihood of a positive SI-MRI in patients with early IBP [4]. Additionally, HLA-B27 has been associated with anterior uveitis in SpA patients [10].

The relevance of MRI and HLA-B27 as central parameters in defining the spectrum of SpA is obvious for many reasons: First, these parameters have been included in the classification criteria: HLA-B27

in Amor criteria [11] and both (SI-MRI/ HLA-B27) in the ASAS classification criteria. In the ASAS axial-SpA criteria [12], two "anchor criteria" were defined in combination with SpA features: the "imaging arm" requires the evidence of sacroiliitis by imaging and the "clinical arm" requires the presence of the HLA-B27 antigen. In peripheral-SpA [13], sacroiliitis on MRI and HLA-B27 were included as additional SpA features. Second, sacroiliitis by MRI and HLA-B27 positivity have been selected as feasible screening methods for axial-SpA [14], and have been included in the decision tree of the original and modified Berlin diagnostic algorithm advised to be used by rheumatologists in daily practice [15]. Recently, these two tests were included in the list of parameters of the ASAS-endorsed recommendation for early referral of patients suspected of having axial-SpA by primary care physicians or non-rheumatologists [16]. Moreover, in an international survey about referral, diagnosis and management in axial-SpA [17], rheumatologists reported that they belief strongly in imaging (MRI) and systematically request HLA-B27-typing when evaluating a patient in their daily practice. However, these tests are rather costly, and waiting time for MRI is long in many countries. Therefore, many recommend to pre-select patients for HLA-B27 testing and SI-MRI in order to increase diagnostic yield.

Knowledge about criteria to order MRI and/or HLA-B27 in patients suspected of SpA, is rather limited. Since imaging MRI and HLA-B27 are a fundamental part of the ASAS classification criteria, and are considered important elements in the early referral and diagnosis of patients, it is expected that the decision about whether or not to order one or both of these tests will become increasingly important. Therefore, the aim of the present study was to identify and evaluate the patient´s characteristics associated with the clinical decision to ask SI-MRI and/or HLA-B27 in the diagnostic work-up of SpA in clinical practice.

METHODS

Study design and data collection

A cohort of consecutive patients referred to a single-center rheumatology outpatient clinic in Colombia were included at the first visit to the clinic between January-2002 and June-2010. Detailed information of the cohort has been published previously [18]. Patients with a clinical diagnosis of SpA by one of two rheumatologists considered experts in the field (RV, JL) were selected and included. Patient information was collected based on data from the clinical record. The institutional ethics committee approved this study, conducted under the principles of the Helsinki declaration. Patients signed informed consent to collect, file and use the data.

We collected data related to demographic and clinical parameters such as gender, age at assessment, age at symptoms onset, symptoms at presentation, disease duration and preceding infection. Furthermore, data on past (history) and present (current) SpA features were collected: chronic back pain, IBP, alternating buttock pain, asymmetric oligo-arthritis (predominantly in lower limbs), enthesitis (heel pain), dactylitis (sausage digit), uveitis (confirmed by an ophthalmologist), psoriasis and inflammatory bowel disease (IBD). The rheumatologists assessed the patients and provided the clinical diagnosis categorized by subtypes (AS, undifferentiated SpA, reactive arthritis, psoriatic arthritis and SpA associated to IBD). The number of classification criteria met, which was retrospectively assessed per patient (ESSG, Amor, and ASAS) and the number of SpA features, were included as explanatory variables. The patients' disease characteristics, including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were assessed. The Ankylosing Spondylitis Disease Activity Score (ASDAS) was calculated per patient: ASDAS-ESR and ASDAS-CRP [19].

Outcome measurement

The outcome of interest in the current analyses was the request of SI-MRI or HLA-B27 by the rheumatologists. Information of this outcome was retrieved from the clinical file with a description of the test result as recorded in the medical chart. If information about SI-MRI or HLA-B27 was found, it was considered that this specific test had been requested by the rheumatologist (who decided to ask these test). Sacroiliitis on MRI was defined according to the local experienced musculoskeletal radiologist's interpretation of the presence of active inflammatory changes in the SI-joint [20]. According to usual clinical practice, no central reading was done. The HLA-B27 test was performed locally in the laboratory of immunology.

Statistical analysis

Descriptive statistics were used to calculate mean (± SD) for continuous data and percentages for categorical data. Explanatory variables were "SI-MRI-ordered" (yes vs no) and "HLA-B27-ordered" (yes vs no).

Age at symptom onset, age at assessment, symptoms at presentation and disease duration had less than 20% of missing data. BASFI, BASDAI, ASDAS-CRP, ASDAS-ESR, CRP and ESR had more than 20% of missing data. All other explanatory variables had complete data. In case of missing data, imputation was performed by using the median or mode from the variable's distribution as appropriate, but only variables with complete data in at least 80% of the cohort were included in the multivariable analysis (see below).

Patient´s characteristics were examined per subgroups of SI-MRI ordered (yes vs no) or HLA-B27 ordered (yes vs no) and analysed by univariable analysis (either by chi-square or by t-test if appropriate) followed by logistic regression analysis. Variables with a p-value <0.05 in univariable

analysis were entered in a (backward selection) multivariable analysis if data availability was at least 80%, with SI-MRI ordered or HLA-B27-ordered as dependent variables.

Based on the hypothesis that IBP will primarily lead to ordering SI-MRI in male patients and in those that have short disease duration, interactions of characteristics with gender (male/female) and with disease duration (short/long) respectively were tested. Potentially relevant interactions ($p \leq 0.1$) were found with age of symptoms onset and age of assessment. These interactions were weak, not considered clinically relevant and not reported.

In the logistic regression analysis, the following variables were excluded because of too much missing information (≥20% of the cohort): BASFI, BASDAI, CRP, ESR, ASDAS-CRP and ASDAS-ESR. In addition, IBD and age of symptom onset were excluded because of collinearity. Statistical analyses were performed with SPSS 20.0 and STATA 12.0.

RESULTS

Patients' characteristics

In total 581 patients with a clinical diagnosis of SpA were analysed. Most of them (72%) were males with a mean (SD) age of 34.6 (12.1) years, age at symptom onset of 28 (10.3) years and disease duration of 7.3 (9.7) years. Sixty percent of the cohort had less than 5 years of disease duration. Disease activity was rather high in the patients with axial SpA: BASDAI 5.4 (2.4), ASDAS-ESR 3.0 (0.9), and ASDAS-CRP 2.6 (0.8), and also in patients with peripheral SpA as assessed by the ASDAS-CRP (2.3 (0.9)). Information on SI-MRI and HLA-B27 was available in a varying proportions of the patients, ordered at the instigation of the rheumatologist: of all patients, 137 patients (24%) had SI-MRI and 441 patients (77%) had HLA-B27 testing performed.

Demographic and disease characteristics of patients in whom an SI-MRI was ordered

In univariable analysis, male gender, the number of symptoms at presentation, short disease duration, chronic back pain, IBP, enthesitis, no history of arthritis, no history of psoriasis, lower CRP, ESR and ASDAS-CRP were associated with a request for SI-MRI.

In multivariable analysis, factors remaining independently associated with ordering SI-MRI were IBP (OR = 1.81, CI 95% [1.13–2.90], p = 0.01), enthesitis (OR = 1.57, CI 95% [1.00–2.49], p = 0.04) and the number of symptoms at presentation (OR = 1.27 per additional symptom, CI 95% [1.10–1.47], p < 0.001). Results are shown in Tables 1-2.

Table 1. Comparison of demographic and SpA disease characteristics according to SI-MRI-ordered status (n=581)

Explanatory variables	SI-MRI ordered Yes n=137	SI-MRI ordered No n=444	p-value
Male gender, (%)	87 (63.5)	330 (74.3)	0.01
Age at assessment, (years)*	33.5 ± 11.8 (n=136)	34.9 ± 12.2 (n=329)	0.46
Age symptom onset (≤35 yrs) (%)*	115 (83.9) (n=133)	365 (82.2) (n=329)	0.64
Symptoms at presentation (%)*			
Arthritis	32 (23.4)	173 (38.9)	≤0.001
Enthesitis	8 (5.8)	24 (5.4)	
Back pain	43 (31.4)	180 (40.5)	
Butock pain	4 (2.9)	5 (1.1)	
Several symptoms	48 (35) (n=136)	58 (13.1) (n=335)	
Disease duration (≤5 years) (%)	52 (37.9) (n=131)	123 (27.7) (n=332)	0.02
Chronic back pain, (%)	123 (89.8)	316 (71.1)	≤0.001
IBP, (%)	88 (64.2)	170 (38.2)	≤0.001
Buttock pain, (%)	48 (35)	124 (27.9)	0.11
Arthritis, (%)	88 (64.2)	331 (74.5)	0.01
Enthesitis, (%)	97 (70.8)	235 (52.9)	≤0.001
Dactyilitis, (%)	21 (15.3)	63 (14.1)	0.74
Uveitis, (%)	10 (7.3)	25 (5.6)	0.47
Psoriasis, (%)	2 (1.5)	25 (5.6)	0.04
Infection history, (%)	36 (26.3)	174 (39.2)	0.006
BASFI (≥4) (%)*	103 (75.2) (n=127)	369 (83.1) (n=239)	0.03
BASDAI (≥4) (%)*	113 (82.4) (n=127)	370 (83.3) (n=239)	0.81
ASDAS CRP high (≥2.1) (%)*	111 (81) (n=80)	434 (97.7) (n=59)	≤0.001
ASDAS ESR high (≥2.1) (%)*	125 (91.2) (n=84)	412 (92.8) (n=162)	0.47
CRP (≥5mg/dl) (%)*	12 (8.8) (n=81)	143 (32.2) (n=97)	≤0.001
ESR (≥20 mm/hr) (%)*	86 (62.8) (n=84)	364 (81.9) (n=218)	≤0.001
Diagnostic subtype (%)			
Ankylosing spondylitis	44 (32.1)	125 (28.1)	0.001
Undifferentiated SpA	70 (51.1)	160 (36)	
Reactive arthritis	20 (14.6)	136 (30.6)	
Psoriatic arthritis	2 (1.5)	19 (4.3)	
IBD	1 (0.7)	4 (0.9)	
Number of SpA features	2.2 ± 1.1	1.9 ± 1.1	0.18
Number of criteria met	2.18 ± 0.8	2.05 ± 0.9	0.64

Values are mean ± SD for continuous variables or percentages for categorical variables, unless otherwise specified. p-values were calculated using t-test adjusted for unequal variances for comparison of continuous variables and Chi square test for categorical variables.

IBP, inflammatory back pain, CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, SpA associated to Inflammatory Bowel Disease; SI-MRI, sacroiliac joints magnetic resonance imaging; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score.

* Variables with missing data, n means the number of patients in which these variables are based.

Table 2. Association of demographic and SpA disease characteristics that independently prompt to ordering SI-MRI. Results from a multivariable logistic regression model

	SI-MRI ordered	
Explanatory variables	**OR (95% CI)**	**p Value**
Male gender (male vs female)	0.79 (0.50-1.22)	0.28
Number of symptoms at presentation (per additional symptom)	1.27 (1.10-1.47)	**≤0.001**
Disease duration (per year)	0.90 (0.57-1.41)	0.66
Chronic back pain (yes vs. no)	1.57 (0.72-3.23)	0.26
Inflammatory back pain (yes vs. no)	1.81 (1.13-2.90)	**0.01**
Arthritis (yes vs. no)	0.85 (0.54-1.33)	0.48
Enthesitis (yes vs. no)	1.57 (1.00-2.49)	**0.04**
Uveitis (yes vs. no)	1.08 (0.48-2.41)	0.85
Psoriasis (yes vs. no)	0.25 (0.53-1.20)	0.08
Infection history (yes vs. no)	0.82 (0.49-1.37)	0.46
Diagnostic subtype	1.06 (0.78-1.43)	0.68

SI-MRI, sacroiliac joints magnetic resonance imaging

Demographic and disease characteristics of patients in whom HLA-B27 was ordered

In univariate analysis, the number of symptoms at presentation, the presence of IBP, uveitis, lower CRP, ESR and ASDAS-CRP were associated with a request for HLA-B27 testing.

In multivariable analysis, the single factor remaining independently associated with ordering HLA-B27 was the number of symptoms at presentation (OR = 1.45 per additional symptom, CI 95% [1.24–1.71], $p < 0.001$). Although uveitis was associated in the univariable analysis with a request for HLA-B27, it just missed statistical significance in multivariable analysis (OR = 3.19, CI 95% [0.94–10.87], $p = 0.06$). Results are presented in Tables 3-4.

Table 3. Comparison of demographic and SpA disease characteristics according to HLA-B27-ordered status (n=581)

Explanatory variables	HLA-B27 ordered Yes (n=441)	HLA-B27 ordered No (n=140)	p-value
Male gender, (%)	311 (70.5)	106 (75.7)	0.23
Age at assessment, (years)*	34.4 ± 12 (n=367)	35 ± 12.3 (n=98)	0.70
Age symptom onset (≤35 years) (%)*	361 (81.9) (n=364)	119 (85) (n=98)	0.39
Symptoms at presentation (%)*			
Arthritis	124 (28.1)	81 (57.9)	≤0.001
Enthesitis	25 (5.7)	7 (5)	
Back pain	191 (43.3)	32 (22.9)	
Buttock pain	8 (1.8)	1 (0.7)	
Several symptoms	87 (19.7) (n=373)	19 (13.5) (n=98)	
Disease duration (≤5 years) (%)*	132 (29.9) (n=344)	43 (30.7) (n=89)	0.86
Chronic back pain, (%)	341 (77.3)	98 (70)	0.07
IBP, (%)	207 (46.9)	51 (36.4)	0.02
Buttock pain, (%)	136 (30.8)	36 (25.7)	0.24
Arthritis, (%)	313 (70.9)	106 (75.7)	0.27
Enthesitis, (%)	255 (57.8)	77 (55)	0.55
Dactyilitis, (%)	61 (13.8)	23 (16.4)	0.44
Uveitis, (%)	32 (7.3)	3 (2.1)	0.02
Psoriasis, (%)	17 (3.9)	10 (7.1)	0.10
Infection history, (%)	153 (34.7)	57 (40.7)	0.19
BASFI (≥4) (%)*	353 (80) (n=291)	119 (85) (n=75)	0.19
BASDAI (≥4) (%)*	366 (82.9) (n=291)	117 (83.6) (n=75)	0.87
ASDAS CRP (high) (%)*	407 (92.3) (n=116)	138 (98.6) (n=23)	0.02
ASDAS ESR (high) (%)*	403 (91.4) (n=222)	134 (95.7) (n=36)	0.15
CRP (≥5 mg/dl) (%)*	43 (9.8) (n=142)	112 (80) (n=36)	≤0.001
ESR (≥20 mm/hr) (%)*	333 (75.5) (n=239)	117 (83.6) (n=63)	0.04
Diagnostic subtype (%)			
Ankylosing spondyltis	134 (30.4)	35 (25)	0.13
Undifferentiated SpA	179 (40.6)	51 (36.4)	
Reactive arthritis	108 (24.4)	44 (31.4)	
Psoriatic arthritis	12 (2.7)	9 (6.4)	
IBD	3 (0.7)	1 (0.7)	
Number of SpA features	2.1 ± 1.1	1.8 ± 1.1	0.36
Number of criteria met	2.1 ± 0.9	1.8 ± 1	0.23

Values are mean ± SD for continuous variables or percentages for categorical variables, unless otherwise specified. p-values were calculated using t-test adjusted for unequal variances for comparison of continuous variables and Chi square test for categorical variables.

IBP, inflammatory back pain, CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, SpA associated to Inflammatory Bowel Disease; MRI, magnetic resonance imaging; BASFI, Bath Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score.

* Variables with missing data, n means the number of patients in which these variables are based

Table 4. Association of demographic and SpA disease characteristics that independently prompt to ordering HLA-B27. Results from a multivariable logistic regression model.

	HLA-B27 ordered	
Explanatory variables	**OR (95% CI)**	**p Value**
Male gender (male vs female)	0.85 (0.53-1.36)	0.50
Number of symptoms at presentation (per additional symptom)	1.45 (1.24-1.71)	**≤0.001**
Disease duration (per year)	1.26 (0.77-2.04)	0.34
Chronic back pain (yes vs. no)	0.96 (0.53-1.73)	0.90
Inflammatory back pain (yes vs. no)	1.14 (0.70-1.85)	0.58
Arthritis (yes vs. no)	1.15 (0.70-1.89)	0.55
Enthesitis (yes vs. no)	0.89 (0.58-1.38)	0.62
Uveitis (yes vs. no)	3.19 (0.94-10.87)	0.06
Psoriasis (yes vs. no)	0.71 (0.27-1.83)	0.48
Infection history (yes vs. no)	11.01 (0.61-1.64)	0.96
Diagnostic subtype	0.85 (0.63-1.15)	0.30

DISCUSSION

The result of this study confirm that rheumatologists working in clinical practice order additional tests such as SI-MRI and HLA-B27 cautiously (not in all patients), and base their diagnostic behaviour on clinical clues. Characteristics associated with the decision to order SI-MRI and/or HLA-B27 in clinical practice, were the presence of IBP, enthesitis, the number of symptoms at presentation and uveitis. Of note, gender, disease duration, the presence of peripheral arthritis and/or psoriasis did not independently determine the behaviour of rheumatologists to request SI-MRI and/or HLA-B27 testing.

Apparently certain clinical manifestations are important. 'Clinical clues' make intuitive sense since they may convey the highest probability on a positive test result (either sacroiliitis on MRI or HLA-B27 positivity) and therefore increase efficiency, optimize usage and save costs. This is true especially for AS [21], a disease that has a reportedly strong association with HLA-B27 and is related to the presence of axial manifestations. In contrast, clinicians apparently know that patients presenting with non-inflammatory mechanical back pain, peripheral arthritis or psoriasis for

example, may benefit more from other tests. Physicians do not ask for HLA-B27 (77%) or SI-MRI (only 24%) in all patients but when clinical symptoms are indicative but not confirmatory.

It is also interesting to look at which factors did not contribute. Apparently, clinicians do not base their behaviour (of asking SI-MRI or HLA-B27) on the conventional appreciation that AS is a disease of males. Gender was not a factor that determined a SI-MRI or HLA-B27 request. That is a promising finding in light of the fact that many still consider females with SpA underdiagnosed in spite of findings suggesting that as many females as males may suffer from axial SpA [22].

It is important to mention that this study has only addressed the performance of a test, and not the result of that test. A recent study from the ESPeranza Cohort [23] has assessed the utility of SpA features to anticipate the presence (not the request) of sacroiliitis on MRI or a positive result of a HLA-B27 test in patients with suspected axSpA. They found that IBP according to the ASAS definition plus alternating buttock pain or IBP according to Calin criteria plus awakening in the second half of the night predicted the presence of sacroiliitis on MRI. Our study assigned IBP as a determinant for ordering SI-MRI. Together, these studies confirm that the presence of IBP according to certain expert-criteria not only evokes an SI-MRI-request, but also that this behaviour is rational in that the likelihood of a positive result increases. In analogy, we have found uveitis being predictive of ordering HLA-B27, while in the ESPeranza Cohort uveitis appeared to be the factor related to a positive HLA-B27 (LR+ of 2.6). This finding is also in line with previous studies reporting that a positive HLA-B27 test in a patient presenting with uveitis plus SpA features may increase the likelihood of a diagnosis of SpA [24, 25].

Clinical clues that guide the request of a SI-MRI or HLA-B27 can be useful in clinical practice, because of costs and waiting time for SI-MRI. A practice based on inexpensive and widely available clues may be cost-and time-efficient, and their importance may increase over time.

This study has limitations. First, the design was retrospective. Other factors than those that have been measured could have influenced the likelihood to request a SI-MRI or a HLA-B27-test. Second the study may have suffered from missing data and from the necessary exclusion of variables with too many missing data. There was, for instance, an indication that SI-MRI and/or HLA-B27 has been preferentially requested in patients with increased acute-phase reactants (CRP and/or ESR). A univariate comparison was highly statistically significant, but the variables were missing in too many patients and were excluded from multivariable analysis. The high level of missingness for CRP and ESR suggests anyway that decisions of requesting additional tests are certainly not only based on CRP/ESR. Third, the study only addresses one side of the entire spectrum: patients with a diagnosis of SpA. Patients in whom a diagnosis of SpA was not established, with or without a SI-MRI or a HLA-B27 test, were not taken into consideration. This study can therefore never be interpreted as a diagnostic experiment that tests the value of SI-MRI and HLA-B27. This study only gives insight into the circumstances in which SI-MRI or HLA-B27 are requested. It is very reasonable to assume that expensive and scarce diagnostics such as SI-MRI and HLA-B27 tests are only considered if they may help the clinician to increase the likelihood of a suspected clinical diagnosis, but not if the clinician considers the likelihood of SpA as sufficiently high. In that situation, he may rather refrain from asking expensive and time-consuming tests. These Bayesian principles form the basis of proper clinical reasoning. Finally, all patients of this study came from the same country and even the same centre, which importantly limits the external validity and the extrapolation of the findings to other countries and clinics. The results of this study should be interpreted in this context.

In conclusion, rheumatologists use certain clinical clues to decide if they order expensive and scarce tests in the diagnostic work-up of patients with SpA. These manifestations may increase the efficiency of these tests in clinical practice and suggest that clinical reasoning follows principles of Bayesian theory.

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4

Prevalence of comorbidities and risk factors of spondyloarthritis in Latin America: a comparative study with the general population based on data from the multinational ASAS-COMOSPA study

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ABSTRACT:

Objectives Increased risk of comorbidities has been reported in spondyloarthritis (SpA). The objective of this study was to determine the prevalence and risk of developing comorbidities in SpA-patients in three Latin America (LA) countries, and to compare that prevalence with the general-population.

Methods Data from 390 SpA-patients enrolled in the ASAS-COMOSPA study from Argentina, Colombia and Mexico were analyzed. Age and gender standardized-prevalence (95%CI) was estimated for arterial-hypertension (AHT), tuberculosis (TB), and malignancies. Age-and gender-specific data from general-population were obtained from CARMELA-study for AHT, Global TB-report and GLOBOCAN-project for malignancies. Data analyzed for AHT was confined to Colombia and Mexico. The prevalence in SpA-patients was compared with the prevalence in general-population per age- and gender-specific stratum resulting in standardized risk ratios (SRR).

Results In total, 64% of the SpA patients were male with a mean age of 45(SD 14.7) years. The most common comorbidities in the three LA-countries were, AHT (25.3%, 95%CI 21.2-30.0), hypercholesterolemia (21.5%, 95%CI 17.6-26.0) and osteoporosis (9.4%, 95%CI 6.8-12.9). AHT-prevalence in Colombia and Mexico was 21.4% (95%CI 15.4-28.9) and was increased compared to general-population (12.5%, 95%CI 11.4-13.7) resulting in an SRR of 1.5. TB-prevalence in the three LA-countries was 3.3% (95%CI 1.8-5.7), which was importantly higher than expected from general-population (0.32%), leading to an SRR of 10.3. The prevalence of malignancies was not increased.

Conclusions Patients with SpA in Latin-America are at increased risk of AHT and TB in comparison to the general-population. A systematic evaluation of these comorbidities may help to monitor these conditions.

INTRODUCTION

Comorbidities are frequently associated with inflammatory rheumatic diseases such as ankylosing spondylitis (AS), psoriatic arthritis (PsA) and rheumatoid arthritis (RA). In addition to the musculoskeletal manifestations for SpA and SpA-related extra-articular features (psoriasis, uveitis, inflammatory bowel disease (IBD)), patients may also have an increased risk of cardiovascular (CV) events, metabolic syndrome, malignancies and infections[1, 2, 3]. These comorbidities may result in premature-death[4].

The risk of developing comorbid conditions seems to be higher in patients with SpA than in the general population[5], and these co-morbidities may manifest already shortly after the onset of initial symptoms[6]. CV events occur more frequently in AS patients, likely due to an increased prevalence of traditional risk factors (e.g. metabolic syndrome, arterial hypertension (AHT))[7,8,9] and to the medications used for the treatment of SpA (e.g. non-steroidal anti-inflammatory drugs (NSAIDS). The increased risk of tuberculosis (TB) may be due to immune disturbances by the disease itself and by pharmacological immunosuppression[10]. Additionally, the risk of developing malignancies may be related to chronic inflammation and autoimmunity, although epidemiological evidence that AS is associated with the development of malignancy is lacking [11].

The Assessment of SpondyloArthritis international Society of COMOrbidities in SpA (ASAS-COMOSPA) study [12] is a cross-sectional observational study to assess comorbidities and their risk factors in SpA. This initiative included three Latin American (LA) countries, and provides an opportunity to explore the association of these comorbidities with SpA. While there are data in the literature on comorbid conditions in SpA in other regions, this information is limited in LA countries.

The objective of this study was (1) to determine the prevalence of -and the risks to present -comorbidities as assessed in the ASAS-COMOSPA-study –used as a reference group- in patients with SpA in three LA countries; and (2) to compare the prevalence of these with the information in the general population, in order to find out if the prevalence of -and the risk on -comorbidities is increased.

METHODS

Study design and patient recruitment

This was a cross-sectional study that used data from the worldwide ASAS-COMOSPA-study [12]. Briefly, the ASAS-COMOSPA-study was an observational, multicenter and international study (22 countries from four continents) that included consecutive adult patients who fulfilled the ASAS SpA-criteria (axial or peripheral). The patients in the ASAS-COMOSPA-study enrolled from Argentina, Colombia and Mexico (one academic center in each country) were selected and analyzed for the present study. Additionally, 47 Colombian patients with data that made them eligible to ASAS-COMPOSPA but that were offered after the electronic database for the international study had been locked, were also included in this analysis. The results in which the Global ASAS-COMOSPA study data are reported in this study include the data from the LA countries. The study was approved by the Ethics and Research Committee of the Hospital Militar (No.C-2014-027) and was conducted according to the guidelines for good clinical-practice. All patients sign the informed-consent.

Data collection

Details of the data collection methods have been published previously [12]. A case report form was used in the study to collect the data including patient's demographics, SpA disease characteristics and extra-articular manifestations (uveitis, psoriasis, IBD). Information about past and current

medications (NSAIDs, corticosteroids, conventional-synthetic and biologic-DMARDs) were also collected.

The following comorbidities and risk factors for comorbidities were collected. AHT was defined as a history of AHT or use of anti-hypertensive therapy or a blood pressure at the study visit >140/90. TB was defined as a history or current active TB. Cancer was defined as a history of neoplasia in the colon, skin (melanoma and basocellular-carcinoma), lymphoma (Hodgkin's and Non-Hodgkin's disease), breast and cervix (for women) and prostate (for men). All data were collected by a study investigator by interview and were completed by reviewing medical records. The information was collected and registered in a centralized electronic-case report form.

Data from the general population

Total and gender- and age-group specific prevalence data for AHT of general population were obtained from the Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA-study). This is a population-based observational study (n=11,550) [13, 14] assessing the prevalence of cardiovascular risk-factors in seven Latin American cities including Buenos Aires, Bogotá and México City. The analyses of data of the general population for AHT was confined to Colombia and Mexico. We found a huge inter-country variability with regard to the AHT prevalence in the region, especially the data reported in Argentina. Whereas the AHT prevalence in the general-population in Colombia and Mexico was comparable (13 and 11% respectively), in Argentina the reported prevalence was 29%. Because of this discrepancy, which can be explained by genetic, ethnic and demographic differences between the countries in the region, the analyses for AHT was limited only to these two countries with respect to comparison with general-population.

Prevalence data obtained from the general population of Argentina, Colombia and México were standardized for TB and malignancies. Specific prevalence data for TB stratified for gender and age categories have been obtained for the three countries using the 2015 Global Tuberculosis-report [15]. This report is an initiative of the World Health Organization that provides comprehensive information on the status of the disease at global and country levels. Regarding malignancies, gender- and age-group specific prevalence data have been obtained for the three countries using the 2012 GLOBOCAN-project [16, 17]. This initiative provides prevalence estimates for the major types of cancer worldwide.

Statistical analyses

Descriptive statistics were used for the demographic data, disease characteristics, disease activity, risk factors and the comorbidities of the patients included in the analyses. Data are presented as numbers (%) for qualitative variables and as the mean (SD) for continuous variables. The data were stratified for age categories and for males and females separately by comparing expected (general-population) versus observed (Latin America) frequencies. Data from the Global ASAS-COMOSPA-study was included for comparison with LA countries. In addition 95%CIs were estimated using the method described by Wilson [18], which is considered an accurate and precise method for calculating Cis [19]. Standardised risk-ratios (SRR) were determined to compare event rates (in this study, comorbidities and risk factors) in SpA patients vs. the general-population. SPSS Statistics 22 was used to perform the statistical analyses.

RESULTS

In total, all 390 patients from the three countries Argentina (n=236), Colombia (n=85) and México (n=69) participating in the ASAS-COMOSPA-study were included in the analysis. Patient characteristics including demographic and disease characteristics by country, for the LA countries combined and the global study population -which includes information for the LA countries- are presented in table-1. In the LA countries, sixty-four percent were male, with a mean age of 45 (15) years and a mean disease duration since symptom onset of 7.0 (8.1) years. The proportion of patients with arthritis, enthesitis and dactylitis was higher in the three LA countries (74%, 62% and 24%, respectively) as compared with all patients (n=3,984) in the ASAS-COMOSPA-study (56%, 38% and 16%, respectively). The usage of NSAIDS and DMARDS (particularly methotrexate) was higher in LA countries than in the entire ASAS-COMOSPA-study (72% and 48% respectively for NSAIDS, and 68% and 33% respectively for DMARDS), whereas biological therapy was less frequently used (34% vs 44% respectively). The most common comorbidities and risk factors in all three LA countries were: AHT (25.3%)(95%CI 21.2 to 30.0), hypercholesterolemia (21.5%)(95%CI 17.6 to 26.0), osteoporosis (9.4%)(95%CI 6.8 to 12.9) and gastrointestinal ulcer (7.7%)(95%CI 5.3 to 10.9).

Table 1. Demographic, disease characteristics and comorbidities of the Latin America countries and the global ASAS-COMOSPA study

Characteristic	**ASAS-COMOSPA**	**Latin America**	**Argentina**	**Colombia**	**México**
Number of patients	3984	390	236	85	69
Male gender	65.0	63.8	61.9	60.0	75.4
Age (years)	44 (14)	44.6 (14.7)	45.4 (14.5)	44.1 (13.9)	42.6 (16.3)
Education level (university)	42.4	42.6	34.7	50.6	59.4
Smoking status (current)	23.0	16.7	22.0	10.6	5.8
Disease duration (years)	8.2 (9.4)	7.0 (8.1)	6.7 (8.3)	5.2 (5.6)	9.3 (8.7)
Disease symptoms					
➢ Axial involvement	88.7	84.2	78.3	92.9	94.0
➢ Arthritis	56.4	73.9	77.0	70.6	67.2
➢ Enthesitis	38.0	62.5	57.9	77.6	59.7
➢ Dactylitis	15.6	23.8	25.5	24.7	16.4
➢ Uveitis	20.3	15.8	14.9	11.8	23.9
➢ Psoriasis	22.5	23.0	33.2	4.7	10.4
➢ IBD	5.2	3.3	3.4	3.5	3.0
ASDAS-CRP	2.0 (1.1)	1.9 (1.1)	1.8 (1.1)	2.0 (1.0)	1.8 (1.4)
BASFI	3.0 (2.7)	3.4 (2.8)	3.1 (2.8)	4.3 (2.2)	3.7 (3.0)
NSAIDS use (last 3 months)	67.8	71.8	71.9	68.2	76.1
Methotrexate (ever)	32.7	47.6	48.7	42.3	50.7
Sulfasalazine (ever)	43.9	43.5	25.4	70.2	87
Biological (TNFi) (ever)	43.9	34.1	35.6	36.4	26.1

All values are N (%) *or* mean (SD) for categorical and continuous variables, respectively
IBD, inflammatory bowel disease

Prevalence of comorbidities and risk factors

The prevalence of AHT limited to SpA patients in Colombia and Mexico was higher (21.4%, 95%CI 15.4 to 28.9) as compared to the general-population (12.5%, 95%CI 11.4 to 13.7) in these two countries. The prevalence of AHT was higher in men than in women, especially in the stratum of 55-64 years (57% vs 11%, respectively) and also in patients ≥65 years (70% vs 25%, respectively), in whom cardiovascular risk is expected to be more similar in both genders. Additionally, in young patients (25-44 years) the prevalence of AHT was consistently increased in both genders compared to the general-population. All of these findings were consistent with the prevalence data of the global ASAS-COMOSPA-study. The total AHT risk of patients with SpA in Colombia and Mexico between 24 and 64 years was increased (SRR: 1.5) compared to the general-population. This risk

was increased in women and in men (1.5 and 1.4 respectively) and consistent across different age groups, except in the stratum of 55-64 years in which the risk in women was lower. Detailed data on the prevalence of AHT compared to the general-population are shown in table-2.

Table 2. Observed prevalence of AHT in the ASAS-COMOSPA study (Latin America*) compared with the expected prevalence in general population and prevalence of Global ASAS-COMOSPA for reference.

		Observed LA* ASAS-COMOSPA		Expected General population	**SRR ** (CI 95%)**	Global ASAS-COMOSPA	
Gender	Age	n	(%)	Prevalence (%)		n	(%)
Men	≤24	0	0	NA	-	3	2.65
	25-34	4	12.5	3.6	3.4	49	8.47
	35-44	2	8.7	7.8	1.1	152	24.4
	45-54	6	28.5	14.6	1.9	247	43.3
	55-64	4	57.1	30.9	1.8	240	61.1
	≥65	7	70.0	NA	-	201	84.1
	Total	23	22.3	12.9	1.4 (0.9-2.2)	892	34.4
Women	≤24	0	0	NA	-	0	0
	25-34	1	8.3	0.9	9.2	17	7.4
	35-44	2	15.3	3.8	4.0	61	16.8
	45-54	5	41.6	17.0	2.4	132	36.8
	55-64	1	11.1	34.3	0.3	104	45.6
	≥65	1	25.0	NA	-	102	68.6
	Total	10	19.6	12.1	1.5 (0.8-2.8)	416	29.8
Total (men/women)		33	21.4	12.5	1.5 (1.0-2.1)	1308	33.1

n=number with a diagnosis of arterial hypertension in each gender and age group
Prevalence (%); LA*, Latin America (Data confined to patients from Colombia and México); **SRR, standardized risk ratio (ratio calculated for the age of 25-64 years); NA, not available
Hypertension defined as a history of hypertension or antihypertensive therapy use or blood pressure ≥140/90 mm Hg at the study visit.

The distribution of TB prevalence and risk is presented in table-3. Overall, the observed prevalence of TB infection in LA patients with SpA in the three countries was 3.3% (95%CI 1.8 to 5.7), which was much higher than expected from the general population (0.32%) in these three LA countries and also higher than the prevalence data of the global ASAS-COMOSPA-study (2.5%) (95%CI 2.0 to 3.0).

TB prevalence in LA was lower in men than in women (2.8 vs. 4.2% respectively); in contrast to the global study in which the prevalence was higher in men (3.0 vs. 1.6% respectively). Cases of TB in LA were observed after the age of 35 and homogeneously distributed among all age groups regardless of gender (in total: 7 cases of TB in males and 6 cases in females). Seven of these cases were reported in Argentina and six in Colombia. In contrast in the ASAS-COMOSPA-study, TB cases were reported as early as at an age of 25 years and were more frequent in men (78 male and 23 female cases). The average risk of TB was 10.3 times higher in SpA patients than in the general-population. The risk was more increased in women than in men (18.2 vs. 6.8 respectively) and was found in all age categories except in patients ≥65 years in whom the risk declined in both genders.

Table 3. Observed prevalence of TB in the ASAS-COMOSPA study (Latin America*) compared with the expected prevalence in general population and prevalence of Global ASAS-COMOSPA for reference.

		Observed LA ASAS-COMOSPA		Expected General population	**SRR (CI 95%)**	Global ASAS-COMOSPA	
Gender	Age groups	n	(%)	Prevalence (%)		n	(%)
Men	20-24	0	0	0.29	-	0	0
	25-34	0	0	0.21	-	16	2.7
	35-44	2	3.3	0.23	14.3	15	2.4
	45-54	2	4.3	0.40	10.7	18	3.1
	55-64	2	7.4	0.73	10.1	12	3.1
	≥65	1	4.0	1.14	3.5	17	7.1
	Total men	7	2.8	0.41	6.8 (3.2-13.9)	78	3.0
Women	20-24	0	0	0.22	-	0	0
	25-34	0	0	0.13	-	1	0.4
	35-44	2	5.6	0.15	37.3	4	1.1
	45-54	1	2.8	0.19	14.7	6	1.7
	55-64	2	7.4	0.37	20.0	11	4.8
	≥65	1	7.1	0.41	17.3	1	0.7
	Total women	6	4.2	0.23	18.2 (8.5-40.6)	23	1.6
Total men/women		13	3.3	0.32	10.3 (6.1-17.8)	101	2.5

n= number with a history or current active TB
Prevalence (%); SRR, standardized risk ratio; LA*, Latin America

The malignancies found in SpA patients in men were: prostate-cancer (n=2), skin-cancer (n=2), colon-cancer (n=1); and in women: cervix-cancer (n=2), breast-cancer (n=2) and skin-cancer (n=2). The majority of cases had been reported in patients ≥50 years of both genders, (7 cases in Argentina, 3 cases in Colombia and one case in Mexico). The overall prevalence of malignancies observed in the three LA countries was 2.8% (95%CI 1.4 to 5.1), which was slightly lower than the prevalence in the global ASAS-COMOSPA-study (3.2%, 95%CI 2.6 to 3.8) and not significantly increased in comparison to the general-population (2.6%) (p=0.5). The SRR for malignancies was 1.0. There was not a significant increase in the prevalence and the risk to develop malignancies in patients with SpA compared with the general-population (Table-4).

Table 4. Observed prevalence of all malignancies in the ASAS-COMOSPA study (Latin America) compared with the expected prevalence in general population and prevalence of Global ASAS-COMOSPA for reference.

		Observed LA ASAS-COMOSPA		Expected General population	**SRR (CI 95%)**	Global ASAS-COMOSPA	
Gender	Age groups	N	(%)	Prevalence (%)		n	(%)
Men	20-39	0	0	0.41	-	4	0.3
	40-44	0	0	0.76	-	2	0.6
	45-49	0	0	1.29	-	5	1.6
	50-54	1	5.0	2.39	2.0	8	3.0
	55-59	1	7.6	4.11	1.8	9	3.9
	60-64	1	7.1	6.49	1.0	9	5.4
	65-70	1	8.3	9.28	0.8	13	11.3
	≥70	1	7.6	15.17	0.5	27	21.9
	Total men	5	2.0	2.41	0.8 (0.3-1.9)	77	2.9
	20-39	0	0	0.54	-	6	1.2
	40-44	0	0	1.91	-	3	1.6
	45-49	1	4.3	2.70	1.5	4	2.2
	50-54	2	15.3	3.53	4.3	11	6.0
Women	55-59	2	13.3	4.49	2.9	6	4.6
	60-64	1	8.3	5.90	1.4	10	10.0
	65-70	0	0	6.98	-	4	4.8
	≥70	0	0	9.57	-	7	10.7
	Total women	6	4.2	2.67	1.5 (0.7-3.4)	51	3.6
Total (men /women)		11	2.8	2.6	1.0 (0.6-1.9)	128	3.2

n=number with a diagnosis of malignancies in each gender and age group.
Prevalence (%). SRR: Standardized risk ratio; LA*, Latin America

DISCUSSION

The results of this study show that the prevalence and the risk of ATH and TB is increased in patients with SpA if compared to the age- and gender-adjusted general-population in LA. Of note, the prevalence and the risk to develop malignancies were not significantly increased in SpA patients in comparison to the reference population.

Studies assessing the prevalence of AHT in AS patients have yielded different results. These discrepancies could be explained by the heterogeneity of study populations investigated [20]. A cross-sectional US analysis [21] of the risk factors of CV disease showed an increased prevalence ratio of AHT in AS (1.3 [95%CI 1.1-1.4]) compared with control subjects (27% vs. 22%). Similar rates were observed in patients with PsA in this study. In a recent Dutch study a higher prevalence of AHT, stratified by age and gender, was observed in AS patients (41%) than in the general population (31%) [22]. Furthermore, a Canadian study has shown that AHT was more common in AS patients (23%) than in matched controls without AS (18%) [23]. Our results are consistent with these studies, reporting a higher AHT prevalence in patients with SpA as compared to a reference population of non-SpA individuals. In contrast, a Swedish study did not find a substantial difference between AS patients and controls regarding AHT (32% vs 29%, respectively) [24]. While chronic inflammation may have had a detrimental effect on endothelial function and may have accelerated the progression of atherosclerosis, the common use of NSAIDS that we found in the current study (72%) is a more likely explanation for the increased prevalence of AHT.

A significantly higher prevalence and risk of developing TB in patients with SpA was found. Genetic factors favouring disease reactivation from latent TB or progression of the infection in addition to conventional risk factors for TB (e.g., age, gender, socioeconomic status, and occupation) may

explain this finding. Additionally, it is also challenging to relate the increased prevalence of TB to the immune disturbances caused by the disease itself, which may also contribute to the risk of developing TB. This increased rate of TB has been observed previously in the early stages of disease in patients with SpA [6] and was expected to be present also in patients with longer disease duration (and longer exposure to inflammation), as in the current study (mean disease duration of 7.0 years). Previous studies in anti-TNF naïve RA patients have shown an increased risk of developing TB (ranging from a 4-fold to a 7-fold increase) compared with the general population [10], suggesting that uncontrolled and chronic inflammation predisposes to TB.

Although some studies have reported that the overall prevalence of TB is lower in women, plausible reasons to explain such a differential effect remain obscure. Factors such as differences in the progression from infection to clinically manifest disease, differences in immune system responsivity and biological differences in disease presentation may be part of the explanation [25]. Although the incidence of TB in LA has declined in the last two decades, the region is still considered an endemic area for TB, mainly due to the presence of social factors that predispose to the disease [26]. In general, these factors increase the exposure to TB-bacilli.

The risk of developing a malignancy was not significantly increased in SpA patients in comparison to the general population. This finding is consistent with previous studies reporting that the overall risk of malignancies was not significantly higher in AS and PsA patients, including those treated with DMARDs or TNF-inhibitors [27]. While malignancies are not rare in patients with AS, there is not a biologically plausible reason to expect a higher risk of cancer in these patients [12].

Previous studies in LA have assessed the prevalence rates of comorbid conditions, especially in RA. A systematic literature review evaluating CV risk factors in RA patients [28] found that AHT was the most common finding in almost all studies performed in the region, with an overall prevalence of 28% (range 11.2% to 80.6%). In our study, we found a prevalence of AHT in SpA patients of 25.3%, in the three LA countries, which was higher than expected from the general population but still lower than the prevalence reported in RA. This finding is consistent with the data observed in AS patients, in whom CV risk factors are less manifest than in RA[8]. Regarding TB data in LA, a recent prospective Brazilian study of patients with chronic inflammatory arthritis including AS, RA and PsA has suggested that patients who start TNF blockers have a significantly higher rate of active TB than healthy-controls (87 vs 36/100,000 person-years) [29].

This study has limitations. First, the sample of patients may not be generalizable to the patient population in each country or the whole region. This cohort may not have been fully representative of all SpA patients in the participating countries; moreover, the sample was rather small (especially for Colombia and Mexico) and limited to those patients that had access to specialized rheumatology care in academic centers. In particular, the higher educational status in Mexico and Colombia gives rise to the suggestion that the sample that was investigated may not be entirely representative of the population of SpA patients in these countries. This should be taken into account when interpreting the results.

In addition, the patients in this study were from only three LA countries, namely those that participated in the international ASAS-COMOSPA-study. Moreover, data of Argentina with regard to AHT was not included in the analyses for comparison to general population and calculation of SRR. It was mainly due to a high inter-country variability of data in the general population as a result of

ethnic and demographic differences; therefore, the AHT data was analysed only for two countries. This limits the ability to extrapolate findings to the whole region. Second, the prevalence of some comorbidities might have been underestimated, because patients may have been unable to participate due to clinically relevant conditions. On the other hand, comorbidities might have been overestimated because of investigation bias: SpA patients with comorbidities that are known to be associated with the disease may be overrepresented in this sample. Finally, it is important to mention an additional source of potential bias in relation to TB-case-ascertainment: While the global TB report had been based on comprehensive data reported at the national level according to guidelines by the World Health Organization, in the COMOSPA study cases of TB had been ascertained by the patients and subsequent medical record review. These data do not necessarily yield the same results.

In conclusion, LA patients with SpA have an increased risk of developing AHT and TB compared with the general-population. These findings illustrate the need for optimal detection and monitoring of these conditions in SpA patients, and have implications for rheumatologist's health assessments, prevention and treatment planning in LA countries.

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5

Is there a relationship between Spondyloarthritis and Periodontitis? A case-control study

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ABSTRACT

Objective To compare the frequency and severity of periodontitis in SpA-patients with healthy-control individuals, through the evaluation of clinical, serological and microbiological periodontal condition.

Methods Patients with a diagnosis of SpA (n=78) and bDMARD-naive fulfilling the ASAS classification criteria as well as 156 healthy-controls matched for age/gender, were included. Two trained and calibrated periodontologists performed the periodontal clinical assessment. The presence of periodontitis and its severity were determined according to the criteria established by the Center for Disease Control and Prevention-American Academy of Periodontology (CDC-AAP). The clinical periodontal variables, IgG1/IgG2 antibodies against *P. gingivalis and* periodontopathic bacterial identification, were also established. Comparisons of periodontal characteristics between the SpA-patients and the control-group were performed using univariable analyses. A logistic regression analyses was performed to calculate the odds ratio (95% CI) for diagnosis of periodontitis in SpA-patients and matched-controls.

Results A diagnosis of periodontitis was established in 56% in SpA patients vs. 69% of healthy-controls (p=0.01)**.** Severe periodontitis was found in 3% vs 12% in SpA vs healthy-controls respectively (p=0.01)**.** There was no significant increase of frequency of any periodontal variable, IgG1/IgG2 antibodies against *P. gingivalis* or the presence of periodontopathic bacteria between SpA patients and control-group. Periodontitis was not positively associated with a diagnosis of SpA (OR: 0.57 95% CI 0.32-1.00, p=0.05) in the logistic regression analyses.

Conclusions We found a lower rather than a higher frequency and severity of periodontitis in SpA patients in comparison to healthy-control individuals. Our findings suggest that there is no positive association between SpA and periodontitis in Colombian patients.

INTRODUCTION

Spondyloarthritis (SpA) is a chronic rheumatic disease presenting with axial (axSpA) and peripheral (pSpA) manifestations [1]. This condition that is characterized by inflammation of the spine and peripheral joints has been associated with other inflammatory diseases such as uveitis, psoriasis and inflammatory bowel disease [2, 3]. Chronic periodontitis is a common worldwide and chronic inflammatory condition characterized by progressive destruction of periodontal ligament and alveolar bone [4].

Results from studies point towards a potential relationship between periodontitis and systemic rheumatic diseases, in particular rheumatoid arthritis (RA) [5]. Studies have found that the presence of RA has been associated with an increased prevalence of periodontitis and also with a significant inflammatory periodontal involvement in early-disease [6, 7]. Periodontitis has been considered as a condition that influences the risk of developing RA in first-degree relatives [8]. Moreover, important mechanisms that characterize the pathogenesis of RA are also involved in the pathogenesis of periodontitis [9]. Many studies have suggested that extra-articular citrullination is an immunological event that may occur in periodontal tissue under inflammatory conditions [10]. Following this reasoning, the citrullination and the induction of anti-citrullinated peptide-antibodies (ACPAs) has emerged as a biochemical-process that may initiate the cascade of events leading to inflammation in RA [11].

Knowledge of the existence of an epidemiological association between SpA and periodontitis may fuel pathophysiological thinking about SpA and if established, have clinical implications. Currently, it is unclear whether SpA patients have a higher frequency of periodontitis and data in the literature reporting a possible association is limited. Therefore, the aim of the present study was to compare the frequency and severity of periodontitis in SpA-patients with age/gender matched healthy-individuals, through the evaluation of the clinical, serological and microbiological periodontal condition.

METHODS

Study subjects

Consecutive adult patients with a diagnosis of SpA (n=78) and fulfilling ASAS classification-criteria [12, 13] attending a rheumatology outpatient-clinic in an academic-center for routine care in Colombia were selected. A control group of 156 individuals from the general population (between 18-65 years) matched for gender and age (maximum difference of one year) were enrolled. Healthy individual volunteers were selected from the same hospital or geographical area. All controls were specifically questioned and were excluded from this study if they reported a history of rheumatologic diseases. Exclusion criteria for cases and controls were use of antibiotics during the last 3-months and a history of periodontal or orthodontic therapy. All individuals completed a specific questionnaire addressing medical history, demographics, body mass index (BMI), and smoking. Information related to current and previous treatment was collected. Disease activity in patients with SpA was assessed using the Ankylosing Spondylitis Disease Activity Score (ASDAS) for CRP [14]. As TNF-alpha has an important role in the pathogenesis of periodontitis and TNF blockers have been considered as a factor that may influence the periodontal condition, all SpA patients included in this study were bDMARD-naive. The institutional ethics-committees approved the study and study subjects provided written informed-consent.

Periodontal assessment

Two trained and calibrated periodontologists with intrareader and interreader agreement ≥0.9 with the standard, performed the periodontal clinical-assessment [15]. Periodontologists were blinded to the group category of the individuals (patients or controls) at the time of evaluation. Each patients and/or control was examined by one of both periodontologist, and each periodontologist assessed about half of the patients and controls. Using a North-Carolina® probe (Hu-Friedy PCPUNC-15), a full-mouth examination at six-sites on each permanent tooth was performed. The periodontal variables assessed were as follows: clinical attachment loss (CAL), pocket probing depth (PD), insertion level total mouth, plaque index and gingival index.

The presence of periodontitis and its severity were defined according to the criteria established by the Center for Disease Control and Prevention-American Academy of Periodontology (CDC-AAP) [16]. According to these criteria, the definitions were based on measures of CAL and PD at the four interproximal sites per tooth. Periodontitis was defined as ≥2 interproximal sites with CAL ≥4 mm or ≥2 interproximal sites with PD ≥5 mm (not on same tooth). Severe periodontitis was defined as ≥2 interproximal sites with CAL ≥6 mm (not on same tooth) or ≥1 interproximal sites with probing depth ≥5 mm.

Laboratory testing

The protocol employed for the detection of IgG1/IgG2 antibodies against *Porphyromonas gingivalis* (P. *gingivalis*) has been previously standardized [7]. To detect these antibodies an indirect ELISA was performed in-house in 96-well plates. Each well was coated with 5 mg of a sonicated preparation of whole *P. gingivalis* ATCC33277 and W83 strains. For bacterial identification the following procedure was performed: after removing supragingival plaque with curettes and previous relative isolation with cotton rolls, a tip of sterile paper (caliber 40-NewStetic) was placed in the gingival sulcus for 20 seconds in 6 of the deepest sites of each patient. The paper tips of each site were placed in a sterile tube and processed for bacterial by quantitative polymerase chain reaction [17]. The results for plaque samples were projected on the standard curve generated with *P. gingivalis* (ATCC 33277), *T. denticola* (ATCC 35405) and *T. forsythia* (ATCC 43037) and transformed to Log10.

Statistical analysis

Descriptive analyses were used to calculate means (SD) for continuous data and percentages for categorical data. The frequencies of periodontitis, severity, periodontal variables, IgG1/IgG2 antibodies against *P. gingivalis* and bacterial identification were established. Comparisons of periodontal characteristics between SpA patients and control individuals were performed using univariable analyses. For variables with a normal distribution, parametric t tests were used. For variables with a non-normal distribution, differences between cases and controls were compared by McNemar test for categorical variables or Wilcoxon signed test for continuous variables. A logistic regression analysis was performed with the diagnosis of periodontitis as a dependent

variable. Odds ratios with 95% confidence interval were calculated. All analyses were performed at a significance level of 5%. The statistical package STATA version 12 was used.

RESULTS

Demographics and clinical characteristics

In total 78 patients in the SpA group and 156 individuals in the healthy control group were matched by age and gender. In the SpA group the mean age was 39.6 (11), 60% were men and the distribution by subtypes was as follows: ankylosing spondylitis (AS) (n=25), non-radiographic axSpA (nr-axSpA) (n=41) and pSpA (n=12). Patients with SpA had a mean disease duration of 5.0 (7.1) years and ASDAS of 2.7 (0.8). Of the SpA patients 45% was HLA-B27-positive. In total, 82% of SpA patients were receiving nonsteroidal anti-inflammatory drugs (NSAIDS) and 49% were receiving sulphasalazine.

Periodontal clinical assessment

In the group of SpA, 56% had a diagnosis of periodontitis, compared with 69% in the control group (p=0.01), according to the parameters of the CDC/AAP. In total, 2.6% had severe periodontitis in contrast to 12.2% in the control group (p=0.01). CAL was less severe in SpA (1.9 (0.6) mm) as compared to controls 2.4 (0.8) mm (p=<0.001). Additionally, the total in-mouth insertion level was found to be lower in SpA patients 2.4 (0.5) mm in comparison to their matched controls 2.9 (0.8) mm (p=<0.001). Results are presented in table 1. In the logistic regression analyses, periodontitis was not positively but negatively associated with SpA (OR=0.57, CI 95% [0.32–1.00], p=0.05).

Antibodies and bacterial identification

There was no significant increase of frequency with regard to IgG1 / IgG2 antibodies against *P. gingivalis* and the presence of periodontopathic bacteria between SpA patients and healthy controls (Table 1).

Table 1 Characteristics and periodontal variables in patients with spondyloarthritis (SpA) and healthy controls

Characteristics	SpA (n=78)	Controls (n=156)	p-value
Age (years)	39.6 (11.0)	39.5 (11.1)	ǂ
Male gender N (%)	47 (60.3)	94 (60.3)	ǂ
Smoking (currently) N (%)	11 (14.1)	14 (9.0)	0.14
Obesity (BMI ≥30) N (%)	6 (7.6)	16 (10.2)	0.43
Periodontitis (positive)* N (%)	44 (56.4)	108 (69.2)	0.01
Severity of Periodontitis* N (%)			
Any	34 (43.6)	48 (30.8)	0.01
Mild	11 (14.1)	20 (12.8)	
Moderate	31 (39.7)	69 (44.2)	
Severe	2 (2.6)	19 (12.2)	
Insertion level total mouth (mm)	2.4 (0.5)	2.9 (0.8)	<0.001
CAL average interproximal (mm)	1.9 (0.6)	2.3 (0.8)	<0.001
Total pocket depth mouth (mm)	3.3 (1.7)	3.2 (1.9)	0.29
Plaque Index (%)	0.4 (0.2)	0.5 (0.2)	0.12
Gingival index (%)	0.3 (0.2)	0.4 (0.5)	0.33
Number of teeth present	26.1 (4.1)	25.5 (5.4)	0.79
P. gingivalis (presence) N (%)	23 (29.4)	71 (45.5)	<0.01
T. denticola (presence) N (%)	13 (16.6)	84 (53.8)	<0.001
T. forsythia (presence) N (%)	6 (7.6)	75 (48.1)	<0.001
IgG1 anti *P. gingivalis* (positive) N (%)	40 (51.2)	80 (51.2)	1
IgG2 anti *P. gingivalis* (positive) N (%)	41 (52.5)	74 (47.4)	0.32

All values given as mean (SD) unless specified;
ǂ Age and gender were matching criteria
*Criteria and severity definition according to the Center for Disease Control and Prevention-American Academy of Periodontology (CDC-AAP)
BMI, body mass index; CAL, clinical attachment loss

DISCUSSION

The results of this case-control study suggest that –unlike the situation in RA- there is not a positive association between SpA and periodontitis in Colombian patients. We even found a lower prevalence of periodontitis and less severe periodontitis in comparison to healthy controls. Moreover, all periodontal characteristics evaluated including clinical parameters, antibodies anti *P. gingivalis* and bacterial identification were not increased in SpA patients as compared to controls.

Several studies on the association between periodontitis and RA have been published [18]. Periodontitis has been considered a condition with an increased prevalence in individuals with RA

and also has been related to the progression of inflammatory involvement in these patients [19]. In contrast, in the current study we did not find a relationship between SpA and periodontitis. Patients with SpA do not share the same genetic risk factors, female predominance and disease-specific autoantibodies such as ACPAs with RA. The citrullination of proteins, which has been suggested the "link" behind the association between RA and periodontitis, is a biochemical process that has not been found relevant in the pathogenesis of SpA [20]. Moreover, the prominent role of HLA-B27 in SpA has not been involved in the pathophysiology of periodontitis. To our knowledge there is no data evaluating the potential contribution of the allele HLA-B27 in the pathogenesis of periodontitis.

A potential association between SpA and periodontitis has been investigated in previous studies. In a study including 51 patients with psoriatic arthritis the frequency of periodontitis was similar and statistically not different compared with control subjects (41 vs. 38% respectively) (p=0.90) [21]. In contrast, a case-control study in Germany including 48 patients with AS reported a significantly higher risk of periodontal disease compared to controls (OR= 5.4, CI 95% 1.4-22.0) [22]. However, the case definition of periodontal disease in this study was based on a clinical measure (CAL≥3mm) instead of a clinical diagnosis or established criteria. Moreover, a study using administrative claims data sourced from the National Health Insurance program in Taiwan reported that AS patients are 1.8 times more likely than controls to have a previous diagnosis of chronic periodontitis (OR= 1.8, CI 95% 1.7-1.9). However, all the cases of periodontitis analyzed in this study were sourced from an administrative database, which may be less accurate than a clinical diagnosis made by periodontologists. Recently, a systematic review and meta-analysis including six case-control studies reported a prevalence rate of periodontitis that ranged from 38% to 88% in AS patients vs. a range from 26% to 71% in controls [23]. Although the authors report an increasing risk of AS associated with periodontitis (OR=1.85, CI 95% 1.7-1.9), the potential confounding factors, high level of heterogeneity and methodological weakness among the few eligible studies may limit the interpretation of the results. Moreover, the different case-definitions of periodontitis used in these studies may have influenced the prevalence of periodontitis and hamper to establish clear associations and comparisons between studies.

Our study has strengths and weaknesses. The main limitations are the cross-sectional design, which complicates the generation of causal inferences. Moreover, there is a limited sample size. However, without a signal at all in any of the periodontitis parameters, it is unlikely that a larger sample size would yield fundamentally different results. Among the strengths of this study are the comprehensive periodontal assessment that had been performed, in addition to the serological and microbiological investigations for the comparison of cases and controls. To our knowledge this is one of the first studies assessing the periodontal condition in the full spectrum of SpA including axSpA and pSpA patients. Moreover, all SpA patients included were not previously or currently exposed to TNF blockers. TNF-alpha has an important role in the pathogenesis of periodontitis. Medications such as TNF blockers have been considered as a factor that may influence the risk of periodontitis and even improve the periodontal condition [24]. In this study we have avoided such potential confounding.

A higher percentage of patients were taking NSAIDs and sulphasalazine and the effect of these medications with regard to the modulation of periodontal condition has not been clearly established. While multiple studies have investigated the effect of NSAIDs on the periodontal condition in terms of reducing gingival inflammation and influencing alveolar bone loss [25, 26], more information is needed investigating the role of NSAIDs as modulatory agents of periodontal disease progression in patients with SpA [27, 28].

A point of concern may be the high prevalence of periodontitis in the Colombian general population. A nation-wide population study led by the Colombian Ministry of Health reporting on the oral health status in adults ≥18 years old (ENSAB IV), found a prevalence of periodontitis of 62% [29]. Moreover, a higher percentage of men had periodontitis in comparison to women (67% vs. 58%). This national-data are in concordance with the prevalence found in the control-group in the current study, taking into account that SpA has a male-predominance and the sample had been matched by gender. This finding implies that Colombia may have a higher prevalence of periodontal disease than other countries such as the United States (47%) [30] or Germany (51%) [31]. In this context, country-specific differences with regard to the prevalence of periodontitis in the general population, should be considered in the interpretation and the external validity of our findings.

In conclusion we have found a lower- rather than a higher frequency and severity of periodontitis in SpA patients in comparison to healthy control individuals in a sample of Colombian patients.

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6

Validation and reliability of translation of the ASAS Health Index in a Spanish speaking population with spondyloarthritis

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Submitted

ABSTRACT

Objective To validate a Spanish-language translation of the ASAS Heath-Index (ASAS-HI) testing its reliability, construct validity and responsiveness in Colombian-patients with spondyloarthritis.

Methods Translation was done following a forward-backward procedure. Patients fulfilling the ASAS criteria for either axial or peripheral-SpA participated. Test-retest reliability was assessed by intraclass correlation coefficient (ICC) in patients without treatment changes. In patients who required a therapeutic intervention, responsiveness was assessed using the standardized response mean (SRM). Construct validity was evaluated by Spearman correlation. Internal consistency (Cronbachs-α) and discriminative ability of the ASAS-HI were assessed.

Results Fifty patients were included: 54% male, mean (SD) age 44.8(13.1), symptom duration 15.8(9.7) years, BASDAI 4.6(2.2), BASFI 4.7(2.5), ASDAS-CRP 2.2(1.0). AxSpA was established in 44 patients (AS=30, nr-axSpA=14) and pSpA in 6. The score of the ASAS-HI was 8.2(5.1). The test-retest reliability was good with an ICC of 0.84. SRM was 2.58 (1.75-3.37) in 10 patients with any intervention and 2.94 (2.13-4.24) for 7 patients starting TNF-blockers. Construct validity showed a good correlation between ASAS-HI and pain, BASDAI, BASFI, and ASDAS ($r \geq 0.60$). A high internal consistency was found with a Cronbachs-α of 0.91. ASAS-HI discriminated well between patients with different stages of disease activity (BASDAI and ASDAS). Those with higher disease activity had higher ASAS-HI scores.

Conclusion The Spanish-language translation of the ASAS-HI has proven to be psychometrically valid for Colombian-patients with SpA. This version is available to evaluate the state of health and functioning in these patients and can be used in clinical practice.

INTRODUCTION

The term spondyloarthritis (SpA) is used to describe a disease characterized by axial and entheseal inflammation, as well as extra articular manifestations such as uveitis and psoriasis [1]. Ankylosing spondylitis (AS) is the prototype of SpA and together with non-radiographic axial SpA (nr-axSpA), constitutes the subgroup that is termed axial SpA (axSpA). This group of patients differentiates from peripheral SpA (pSpA) by the predominance of axial- rather than peripheral manifestations as presenting feature [2, 3]. Given the variable course of SpA, the evaluation of health and functioning is increasingly recognized by health care professionals to be an important outcome when assessing the impact of the disease on the patient.

The Assessment of Spondyloarthritis international Society (ASAS) Health Index (HI) has been developed to measure functioning and health in patients with SpA aiming to better describe the impact of disease in these patients [4]. The ASAS-HI is a linear composite measure based on an item pool which has been developed and based on the International Classification of Functioning (ICF) core set for AS [5]. This index forms a unidimensional scale providing a sum score representing a wide spectrum of different levels of functioning and contains 17 dichotomous aspects addressing the following categories: pain, emotional functions, sleep, sexual functions, mobility, self-care, community life and employment. The questions of the questionnaire range from 0 to 17, with a lower score indicating a better health status. Recently, the ASAS-HI has been translated and adapted cross-culturally into 15 languages worldwide [6].

The English version has proven to be valid and reliable for use in patients with SpA [7]. Since validated Spanish patient-reported and composite measures do not exist for assessing the broad impact of health and functioning in SpA patients, the present study aimed to translate and cross-culturally

adapt the English version of the ASAS-HI into Spanish-language spoken in Colombia and to re-assess reliability and construct validity for patients with SpA after translation.

METHODS

Translation and cultural adaptation

Translation and cross-cultural adaptation of the English version of ASAS-HI was performed according to the published recommendations using a standardized operating procedure (forward-backward procedure) [8]. This method consists of the following 5 steps: translation, synthesis of translation, back translation, expert committee review and pre-testing in a field test with cognitive debriefing. First, three persons (all bilingual) with different profiles or background (including non-medical), independently performed a forward translation of the instrument from the original language (English) to the Spanish-language according to the characteristics of our patients. Back translation was then conducted by two independent bilingual native English speakers blinded to the English version. The expert committee agreed upon the final wording of the Spanish version, who examined semantic, idiomatic, experiential and conceptual issues. All the versions of the questionnaire were consolidated to develop a pre-final version for the field test. The final version (Appendix 1) was tested with 10 native patients with axSpA (60% AS and 40% nr-axSpA). The patients completed the questionnaire in a face to face interview with a physician. Each question was discussed with the patient in order to check whether all items had been fully understood and whether the patient had problems with wording, relevance, acceptability, incomplete concept coverage and comprehensiveness of the translation. Notes were taken about the time to complete the questionnaire and whether the patients made comments about specific items when completing the questionnaires.

Participants

A sample of patients from a rheumatology outpatient clinic in Colombia were invited to complete the ASAS-HI. Adult SpA patients fulfilling the ASAS classification criteria either axial or peripheral were eligible for participation. According to the ASAS international validation study [6] a convenient sample was obtained: at least 80% of patients with axSpA and a maximum of 20% with pSpA. Estimated proportion of axSpA patients were approximately 40% with nr-axSpA and 60% with AS. The institutional ethics committee approved the study. Informed consent was obtained from all participating patients.

Assessments

Demographic and clinical information was collected in the first visit (baseline) including age, gender, years of formal education, work status, presenting symptoms, extra articular manifestations and current results of laboratory test for C-reactive protein (for ASDAS) [9]. To assess the different disease aspects of health, patients were asked about their disease duration (symptoms duration), current medication and completed the patient global assessment (NRS), pain (NRS), spinal pain (NRS), the Bath Ankylosing Spondylitis Disease Index (BASDAI) [10], the Bath Ankylosing Spondylitis Functioning Index (BASFI) [11], EuroQol five dimensions questionnaire (EQ-5D) [12], Short Form Survey Instrument 36-Item (SF-36) [13], Hospital Anxiety and Depression Scale (HAD-S) and ASAS-HI.

Reliability

A subsample of patients with no change in treatment (no change in NSAIDS over last week, no change in DMARD or TNF blockers over last 4 weeks) who considered themselves in a stable disease state were invited to complete the questionnaire at home after 4-7 days interval to evaluate reproducibility (reliability arm).

Sensitivity to change

Patients with clinical disease activity who required an important therapeutic intervention because of unacceptable clinical disease activity were invited to complete the questionnaire during a second visit 4-24 weeks after the initiation for NSAIDS and 12-24 weeks after the initiation for DMARDS (methotrexate, sulfasalazine) or TNF blockers (sensitivity arm). Baseline assessments including the questionnaires and clinical assessments were performed in the clinic.

Statistical analysis

Reliability was assessed by the test-retest method at 4-7 days interval for patients who considered themselves in a stable state. It was measured using the intra-class correlation coefficient (ICC) as an estimate of the instrument reproducibility over time -assuming that no modification in health conditions had occurred. For testing *sensitivity to change,* patients were included in the analyses if they report improvement on a global change question. Results obtained before and after treatment were compared and sensitivity to change was measured using the standardised response mean (SRM), which is calculated by dividing the mean score change by the standard deviation (SD) of the change.

Construct validity was analysed between ASAS-HI score and several other health outcomes: patient global, pain, spinal pain, BASDAI, BASFI, ASDAS, SF-36, EQ-5D and HAD-S using Spearman's correlation coefficient (considered good if ≥0.6). *Internal consistency* was evaluated by Cronbach's α coefficients (adequate: ≥0.70) [14].

The discriminant ability of the ASAS-HI was assessed between groups differing in overall health -the four disease activity states according to the ASDAS score [8] (inactive, moderate, high and very high). All statistical tests were two-sided and p values ≤0.05 were considered significant. Statistical analyses was done using SPPS (Chicago, Illinois, USA) version 19.

RESULTS

Translation and cultural adaptation

No major problems for translation and cross-cultural adaptation were observed. Overall, none of the patients had difficulties in answering the ASAS-HI and they felt comfortable with evaluating the questionnaire. Results of the cognitive debriefing demonstrated that the translated version of the ASAS-HI was properly understood. The mean (SD) time to complete the ASAS-HI was 2.55 (0.9) minutes.

Clinimetric properties of the ASAS-HI

Subjects

Fifty patients agreed to participate and completed the questionnaire. The diagnosis was axSpA in 44 patients: AS (n=30) nr-axSpA (n=14) and pSpA in 6 patients. Of these patients, 18 participated in the test-retest reliability study arm and 10 participated in the sensitivity to change study arm. The characteristics of the population are presented in table 1. Fifty four percent of the patients were male, mean age of 44.8 (13.1) years and symptom duration of 15.8 (9.7) years. The mean scores for clinical assessments were: BASDAI 4.6 (2.2), BASFI 4.7 (2.5) and ASDAS-CRP 2.2 (1.0). The total score of the ASAS-HI was 8.2 (5.1).

Table 1 Demographic and clinical features of SpA patients (n=50)

Characteristics	AS (n=30)	Non-radiographic axial SpA (n=14)	Peripheral SpA (n=6)	All SpA (n=50)
Male N (%)	17 (57)	6 (43)	4 (67)	27 (54)
Age (years)	46.0 (14.8)	45.1 (9.0)	38.5 (11.3)	44.8 (13.1)
University education N (%)	12 (40)	4 (29)	0 (0)	16 (32)
Symptom duration (years)	18.9 (9.5)	12.7 (8.6)	7.8 (6.5)	15.8 (9.7)
Patient global (0-10 NRS)	4.8 (2.7)	5.0 (2.3)	4.0 (2.6)	4.8 (2.5)
Pain (0-10 NRS)	4.8 (3.2)	2.6 (2.0)	0.5 (0.7)	4.0 (3.1)
Spinal pain (0-10 NRS)	4.6 (3.3)	3.0 (1.7)	0.5 (0.7)	3.9 (3.1)
BASDAI	4.7 (2.4)	4.5 (1.7)	4.0 (2.9)	4.6 (2.2)
BASFI	5.1 (2.6)	4.3 (1.7)	3.6 (3.0)	4.7 (2.5)
ASDAS	2.3 (1.1)	2.2 (0.7)	2.0 (1.2)	2.2 (1.0)
ASAS-HI	8.4 (5.5)	8.4 (3.2)	6.6 (7.4)	8.2 (5.1)

All values given as mean±SD unless specified

SpA, spondyloarthritis; AS, ankylosing spondylitis; NRS, numerical rating scale; BASDAI, Bath ankylosing spondylitis activity disease indez; BASFI, Bath ankylosing spondylitis functional index; ASDAS, Ankylosing Spondylitis Disease Activity Score, ASAS HI, The Assessment of Spondyloarthritis international Society Health Index

Test-retest Reliability

The mean (SD) baseline ASAS-HI was 8.9 (5.0) and the second ASAS-HI was 7.4 (5.4) in the 18 patients in the reliability arm. The ICC was good 0.84 (95% CI 0.71 to 0.93, p<0.001).

Sensitivity to change

Ten patients required change of treatment: 7 patients started a TNF blocker, 2 patients started NSAIDS and 1 patient a DMARD. The SRM was 2.58 (1.75 to 3.37) for all patients requiring modification of treatment (n=10). For those patients in which the intervention was starting a TNF blocker (n=7) the SRM was higher: 2.94 (2.13 to 4.24) than those starting a NSAID or DMARD (n=3), in which the SRM was 2.22 (1.23 to 3.21).

Construct validity

The ASAS-HI had good correlation with the following disease specific clinical parameters: patient global (r=0.58), spinal pain (r=0.59), pain, BASDAI, BASFI, ASDAS, and HAD-S (r=0.60-0.70) and the highest correlations with EQ-5D and SF-36 (r>0.70). The correlations of ASAS-HI with age and symptom duration were weak. Results are presented in table 2.

Table 2 Correlation coefficient (95% IC) between ASAS-HI score and clinical characteristics (n=50)

	Spearman correlation coefficient	
Characteristics	ASAS-HI score	P value
Age	-0.007	0.96
Symptom duration	-0.11	0.43
Patient global (0-10 NRS)	0.58	< 0.0001
Pain (0-10 NRS)	0.61	<0.0001
Spinal pain (0-10 NRS)	0.59	<0.0001
BASDAI	0.66	<0.0001
BASFI	0.62	<0.0001
ASDAS	0.65	<0.0001
EQ-5D	0.75	<0.0001
SF-36 (physical component)	0.72	<0.0001
SF-36 (mental component)	0.74	<0.0001
HAD-S Anxiety	0.65	<0.0001
HAD-S Depression	0.69	<0.0001

ASAS HI, The Assessment of Spondyloarthritis international Society Health Index; BASDAI, Bath ankylosing spondylitis activity disease index; BASFI, Bath ankylosing spondylitis functional index; ASDAS, Ankylosing Spondylitis Disease Activity Score; NRS, numerical rating scale; EQ-5D, EuroQol five dimensions questionnarie; SF-36, Short form Health Survey 36 items; HAD-S, Hospital Anxiety and Depression Scale.

Internal consistency

ASAS-HI scores showed a high internal consistency with a Cronbach´s alpha of 0.91.

Discriminative ability

Finally, the ASAS-HI was discriminative between the four health states of the ASDAS score (inactive, moderate, high and very high disease activity). The groups with greater disease activity had higher mean ASAS HI scores than those with lower disease activity. Results are given in table 3.

Table 3 Discriminant ability of ASAS-HI stratified by disease activity

	ASDAS status groups			
	Inactive (n=8)	Moderate (n=12)	High (n=19)	Very high (n=5)
ASAS-HI	2.5 ± 5.9	5.9 ± 3.0	9.4 ± 3.9	13.6 ± 2.0
BASDAI	1.2 ± 0.5	3.6 ± 1.0	5.8 ± 1.5	6.8 ± 0.4

All values given as mean±SD

ASAS HI, The Assessment of Spondyloarthritis international Society Health Index; BASDAI, Bath ankylosing spondylitis activity disease index; ASDAS, Ankylosing Spondylitis Disease Activity Score.

DISCUSSION

The translated and culturally adapted version of the ASAS-HI reported in the current study maintains all the properties of the original English-language version of the questionnaire. The procedure implemented to translate the instrument followed a standardized operating procedure according to the recommendations published by Beaton [8]. Further we tested several aspects of its validity, relevance and comprehensibility among patients with SpA. Therefore, the health status and functioning in Spanish-speaking patients with SpA may be properly assessed with the translated version of the original ASAS-HI.

The psychometric properties of this Spanish-language version of the ASAS-HI were consistent with the results found in the original study [6], and also with the study of the validity of the Korean-language translation[15]. The reliability of the adapted version showed a good test-retest reliability

(ICC >0.8) and a high internal consistency (Cronbach-α >0.9). The ASAS-HI was sensitive to pick up changes after starting a new pharmacological treatment. The SRM was higher than those seen in the original description of the instrument, a fact that could be explained by the higher baseline values on the instrument that could imply a higher probability of significant changes after effective treatment. Regarding construct validity, the translated version had good correlation (>0.6) with several clinical parameters used currently to assess function, disease activity and quality of life in patients with SpA. In addition, the instrument was discriminative regarding different thresholds of disease activity.

Some limitations need to be considered. First, when evaluating test-retest reliability, no external and objective measure was included to assess stability of the health condition. However, it is accepted that a seven-day period in a chronic disease is an appropriate interval to avoid a significant variability in health, on the one side, and avoid too much recall bias on the other side. Second, the Spanish-language version of the ASAS-HI validated in the current study is validated for the Colombian population. Regarding other Spanish-speaking populations, the use of this version may require additional cross-cultural adaptation and validation mainly due to linguistic variations and cultural differences. Two additional Spanish-versions of the ASAS-HI are available (Mexico and Spain) and were elaborated independently during the international validation project. The differences with these translated tools are restricted to a few changes in wording. For instance, the original English version asks about problems using toilet facilities. The word “toilet” was translated using different Spanish words in each country. In the same way, “exhausted” was translated using three different words having the same meaning. Similar findings were observed with the translation of the following words: “car”, “hair” and “flat ground”. Although these semantic differences may reflect the transcultural adaptation of the instrument in each country, the underlying concept to

assess functioning remains the same. Third, although the 9 items of the Environmental Factors sets related to the ASAS-HI were additionally translated and evaluated in the field test, the questionnaire was not included in the current study.

Our study contributes to SpA assessment by providing a reliable and valid cross-culturally adapted Spanish-speaking version of the ASAS-HI that is sensitive to change. This adapted instrument may be complementary to previous tools validated in Spanish-language and currently implemented in trials and clinical practice to assess patients with SpA [16, 17].

In conclusion, the Spanish ASAS-HI version represent a relevant and comprehensive patient-based instrument for evaluating the state of health and functioning in Colombian patients with SpA. This version is available and can be used in research and in clinical practice.

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7

How well are the ASAS/OMERACT Core Outcome Sets for Ankylosing Spondylitis implemented in randomized clinical trials? A Systematic Literature Review

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ABSTRACT

Objective: To investigate how well the ASAS/OMERACT core set and response criteria for ankylosing spondylitis (AS) have been implemented in randomized controlled trials (RCTs) testing pharmacological and non-pharmacological interventions.

Methods: A systematic literature search was performed up to June 2013 looking for RCTs in patients with axial SpA (AS and non-radiographic axial SpA). The assessed domains and instruments belonging to the core sets for disease controlling anti-rheumatic therapy (DC-ART) and symptom modifying anti-rheumatic drugs (SMARD) were extracted. Results were reported separately for those trials published until 2 years after the publication of the core set (1 April 2001; 'control trials'), and those trials published at least two years after the publication date ('implementation trials').

Results: One hundred twenty three articles from 99 RCTs were included in the analysis, comparing 48 'control trials' and 51 'implementation trials'. Regarding DC-ART core set, the following domains were significantly more frequently assessed in the 'implementation group' in comparison to the 'control group', 'physical function' (100% vs 41.7%; $p \leq 0.001$), 'peripheral joints/entheses' (100% vs 33.3%; $p \leq 0.001$) and 'fatigue' (100% vs 0%; $p \leq 0.001$). Three instruments were significantly more used in the 'implementation group': BASFI (100% vs 8.3%; $p = \leq 0.001$), CRP (92.3% vs 58.3%; p=0.01) and BASMI (53.8% vs 0%; p=0.001).

Regarding SMARD core set domains, physical function (92% vs 23%; $p \leq 0.001$) and fatigue (84% vs 17%; $p \leq 0.001$), as well as the instruments BASFI (88% vs 14%; $p \leq 0.001$) and BASMI (52% vs 0%; $p \leq 0.001$), increased significantly in the 'implementation group'. Twenty percent of trials from the 'implementation group' but none from the 'control group' included all domains of the core-set.

Conclusion: In conclusion, this study provides evidence for the implementation of the ASAS/OMERACT core-set in RCTs of both DC-ART and SMARD. This applies to the use of the domains and to a lesser extent to the specific instruments.

INTRODUCTION

Spondyloarthritis (SpA) refers to a group of chronic inflammatory rheumatic disorders, and ankylosing spondylitis (AS) is considered the prototype of this group [1]. In an attempt to bring more homogeneity in outcome assessment in AS and facilitate the conduct of clinical trials, the Assessment of SpondyloArthritis international Society (ASAS) has selected core sets of variables to include as standardized end points in clinical trials and clinical practice. These core sets have been endorsed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group [2].

ASAS has defined three scenarios for core-sets: 1) disease controlling anti-rheumatic therapy (DC-ART); 2) symptom modifying anti-rheumatic drugs (SMARD) and physical therapy; and 3) clinical record keeping. The domains selected for all three core-sets include 'physical function', 'pain', 'spinal mobility', 'stiffness', 'fatigue' and 'patient's global assessment'. The core-sets DC-ART and clinical record keeping further include 'peripheral joints/entheses' and 'acute phase reactants' and the core-set for DC-ART includes 'radiographs of the spine'. In addition, specific instruments to assess each of these domains were chosen [3].

It has been postulated that the definition of core-sets and the choice of appropriate instruments, which were effective in 1999 [4], have importantly facilitated the development and successful registration of new treatments in AS. However, it is difficult to prove if, and to what extent, the core-sets have contributed to this. An indirect indication for the value of core-sets in the development of new treatments could be the demonstration that the usage of domains and instruments has measurably increased after the description of the core-sets (implementation). In rheumatoid arthritis, a recent study found evidence of uptake of the core set [5].

However, the implementation of the ASAS/OMERACT core-sets has so far not been evaluated. The main purpose of this systematic literature review, therefore, is to analyze and compare the usage of domains and instruments of the core-sets before and after the publication of the original article (April 1999). In addition, we checked the implementation of ASAS response criteria.

METHODS

In order to ensure the transparent and complete reporting of this systematic review, the PRISMA statement was used as guidance [6]. The research question was structured according the PICOT strategy: population, interventions, control group, outcome and study types. The 'population' was defined as trials in patients with a diagnosis of AS or SpA. The 'intervention group' was defined as trials with pharmacological and non-pharmacological interventions published after April 2001 (the date was defined two years after the publication date to ensure that there was sufficient time to include the core set measures in RCTs). The 'control group' was defined as trials with pharmacological and non-pharmacological interventions published before April 2001. 'Outcome' was defined as the domains and instruments in the core-sets for SMARD/physical therapy and DC-ART. 'Study type' was confined to RCTs.

A systematic literature search was performed in PUBMED Medline and EMBASE electronic library databases to identify target studies using a comprehensive search strategy. The search was updated last on 18 June 2013, without limitation of years of publication.

Search Strategy

Articles in English, French, German, Dutch, Portuguese or Spanish were selected for analysis. All of the descriptions and synonyms for AS and SpA were used in the search terms, in order to identify all relevant studies. Details of search strategy terms for identification of studies can be found online as a supplementary web-Appendix.

Study Selection

Two authors (WB, VN) independently screened each title and abstract in order to select the articles for inclusion in the review. They determined the eligibility of each article according to predefined selection criteria. The main inclusion criterion was: RCT's including patients with AS and/or SpA. Since axial SpA constitutes a new term that includes patients with predominantly axial symptoms of SpA, studies with non-radiographic axial SpA patients were also included. Since some studies have included not only axial SpA patients but also patients with other rheumatic conditions, we have selected those studies in which at least an arbitrary 80% of the patients were axial SpA patients.

If title and abstract provided insufficient information, the full article text was obtained and reviewed. Reasons to exclude studies were: the sole report of outcomes not included in the ASAS core-set; and the impossibility to obtain a full text. Disagreement between the reviewers regarding inclusion of the articles studies was resolved by consensus. The references of all included papers can be found online in the appendix.

Data collection

The same two authors extracted the data from the included studies independently according to a predetermined and standardised outcome review matrix. Differences regarding data extraction were resolved by re-review and consensus discussion by the two primary reviewers. General data extracted included information about first-author, publication year, study start date and end date, study duration, interventions, total number of patients randomized and number of AS/SpA patients and primary outcome. The presence/absence of reported domains collected were: 'physical function', 'pain', 'spinal mobility', 'stiffness', 'fatigue', 'patient global assessment', 'peripheral joints/entheses', 'acute phase reactants' and 'spine radiographs'.

All different instruments and outcomes described in each study were extracted and included in the analysis. The instruments that were noted for each domain were those included in the ASAS core set, as well as additional instruments that were considered belonging to the same domains. Table1 describes the domains and the instruments according to the ASAS/OMERACT core-set, as they were published originally in 1999 and with a minor modification to add additional instruments in 2009 [2, 3].

If the composite measure BASDAI (Bath ankylosing spondylitis disease activity index) was reported, we considered the following domains also as performed: fatigue, pain, stiffness and peripheral joint/entheses, even though these were not separately reported. If the BASMI (Bath ankylosing spondylitis metrology index) was reported, we considered the domain spinal mobility as well as the instruments lateral spinal flexion, tragus-to-wall distance, modified Schober's test, Intermalleolar distance and cervical rotation also as performed, regardless of whether they were separately reported. Additionally, measures for the evaluation of treatment response were

extracted; including the response criteria ASAS20 [7], ASAS40 [8], ASAS5/6 and BASDAI50, and the disease state ASAS partial remission.

Table 1 Assessment of SpondyloArthritis international Society (ASAS)/Outcome in Rheumatology (OMERACT) core set for symptom modifying anti-rheumatic drugs (SMARD), disease-controlling anti-rheumatic treatments (DC-ART) and specific instruments for each domain.

Domains	Instruments van der Heijde, 1999	Instruments ASAS Handbook, 2009
Function	Index (DFI) [10]	BASFI
Pain	VAS, last week, spine, at night, due to AS	NRS/VAS (last week/spine/night/due to AS)
	VAS, last week, spine, due to AS	NRS/VAS (last week/spine/due to AS)
Spinal mobility	Chest expansion [11], modified Schober test [12], occiput to wall distance	Chest expansion, modified Schober, occiput to wall, cervical rotation, (lateral spinal flexion or BASMI) [13]
Spinal stiffness	Duration of morning stiffness, spine, last week	NRS/VAS (duration of morning stiffness, spine, last week)
Patient global	VAS last week	NRS/VAS (global disease activity last week)
Peripheral joint, entheses	Number of swollen joints (44-joint count), no instrument for entheses	Number of swollen joints (44 joint count) MASES [14], San Francisco or Berlin
Acute phase reactants	ESR	CRP or ESR
Radiograph spine	AP/lat lumbar and lat cervical spine and X-pelvis (SI and hips)	mSASSS [15] on lateral lumbar spine / lateral cervical spine
Fatigue	No preferred instrument	Fatigue question BASDAI [16]

BASDAI, Bath Ankylosing Spondylitis Functional Index; NRS, Numerical Rating Scale; VAS, Visual Analogue Scale; BASMI, Bath Ankylosing Spondylitis Metrology Index; MASES, Maastricht Ankylosing Spondylitis Enthesis Score; CRP, C-reactive protein; ESR, Erythrocyte Sedimentation Rate; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; BASRI, Bath Ankylosing Spondylitis Radiology Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

Data Analysis

First, all information retrieved from multiple articles but belonging to the same RCT was combined and considered as one RCT for the analysis. The datasets were analyzed to compare the use of the outcome measures in RCTs before and after the publication of the core-set.

Since the ASAS-endorsed response criteria were published in 2001 (ASAS20 and ASAS partial remission) and in 2004 (ASAS40 and ASAS 5/6), only studies published two years after those dates were included in the assessment of these criteria, in order to give time for the implementation. The number of trials assessing all domains of the core set was analysed for interventions and control group, in trials evaluating interventions with DMARDSs, biologics and glucocorticoids as well as trials with other types of interventions including NSAIDS. In order to illustrate the evolution of the representation of domains and instruments overtime two figures were constructed.

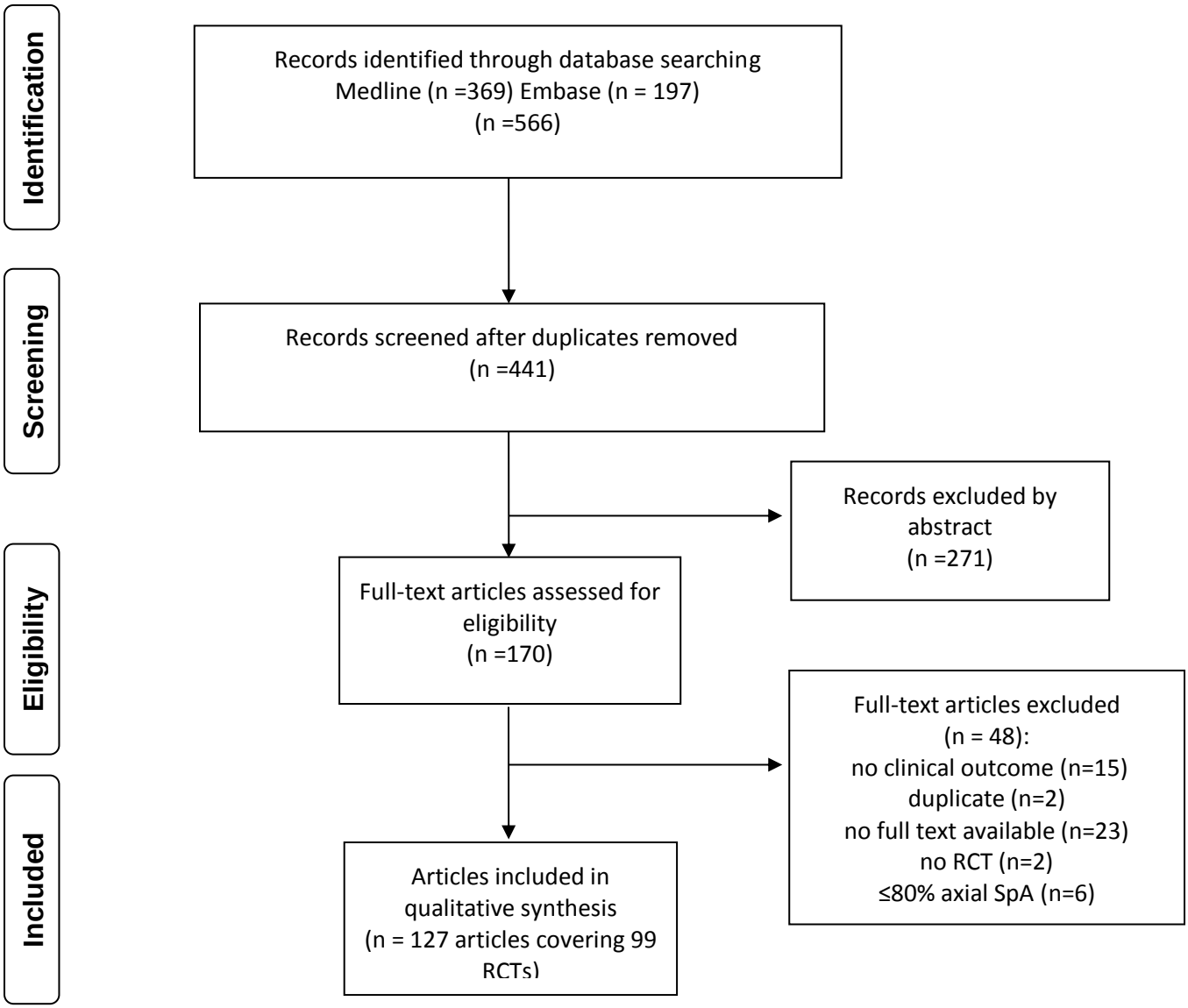
For descriptive purposes, results were presented as means and standard deviations or medians for continuous variables, and as frequencies (percentages) for categorical variables. The Student t-test for independent samples and Chi-square tests (and Fisher test if necessary) were used to compare continuous and dichotomous variables between implementation and control groups, respectively. Statistical analysis was done using SPSS software version 18.0.

RESULTS

Results of the search

The search strategy generated a total of 566 articles. Of these, 127 articles reporting the results of 99 clinical trials fulfilled the eligibility criteria. Reasons to exclude studies are mentioned in the flow chart. An important reason to exclude was that the clinical outcomes we were interested in were not reported (n=15). A summary of the search results is depicted in Figure 1.

Figure 1 Flow chart of the results of the search strategy, describing the reasons for study exclusion.



Characteristics of the RCTs

Forty-eight of the 99 RCTs fell in the group of 'control trials' and 51 in the group of 'implementation trials'. A total of 12,261 patients, 94% (n=11,497) of those having a diagnosis of AS and 2% (n= 251) having a diagnosis of non-radiographic axial SpA, were included in the trials. The remaining patients (4%, n=513) had a diagnosis of another rheumatic condition such as another SpA subtype (psoriatic arthritis, undifferentiated SpA and reactive arthritis), rheumatoid arthritis and osteoarthritis.

The median number of AS patients per trial was similar (60 versus 61) in the 'control' vs the 'implementation group'. Median study duration was slightly higher in the 'control' group in comparison to the 'implementation' group (20 vs 16 week). Trials evaluating the efficacy of NSAIDs (52% vs 8%; p≤0.001) and DMARDs (21% vs 6%; p=0.06), were more frequently found in the 'control' group as compared to the 'implementation' group. However, trials evaluating biological drugs (45% vs 0%; p≤0.001) and also physical therapy (27% vs 10%; p=0.03), were more frequently represented in the 'implementation' group as compared to the 'control' group. The main characteristics of the RCTs in both groups are shown in table 2.

In trials evaluating interventions with DMARDs, biologics and glucocorticoids, 5 out of 26 trials (19%) in the 'implementation group' but none of the trials in the 'control group', included all domains of the core-set. In trials with all other types of interventions -including NSAIDS-, a full set of domains was used in 8 out of 25 trials (32%) of the 'implementation group' and in 1 out of 36 trials (3%) of the 'control group'.

Table 2 Characteristics of Randomized Controlled Trials selected for detailed review

	Control group (before April 2001) (n = 48)		**Implementation group (after April 2001)** (n= 51)		
	mean ± SD	median Min, Max	mean ± SD	median Min, Max	p value ¶
N. patients (n)	117 ± 140	60 (35-140)	131 ± 145	61 (45-185)	0.7
N. Axial SpA patients (n)	114 ± 138	60 (33-134)	126 ± 145	58 (45-154)	0.6
Study duration (weeks)	24.8 ± 27.7	20 (6-36)	24.0 ± 20.6	16 (12-24)	0.8
Intervention	**N**	**%**	**n**	**%**	
NSAIDs	25	52	4	7.8	< 0.001
DMARDs	10	21.3	3	5.9	0.06
Biological drugs	0	0	23	45.1	< 0.001
Glucocorticoids	2	4.3	0	0	0.2
Physical therapy	5	10.6	14	27.5	0.03
Balneotherapy	0	0	4	7.8	0.05
Miscellaneous*	6	12.8	3	5.9	0.4

*Miscellaneous interventions: fish oil capsules, pamidronate, levamisole, amitriptilyne, probiotic oral therapy, formicarufa, cognitive-behavioural therapy. ¶ p values are for comparison between groups.

RCTs evaluating DMARDs, biological drugs or systemic glucocorticoids

Domains

The usage of the domains and instruments recommended for the DC-ART scenario is shown in Table 3. The domains 'patient global assessment' was assessed in about 60% of the trials (61% vs 67%; p=0.8) in 'implementation' and 'control group'. The domain 'spine radiograph' was only assessed in the implementation group (23% vs 0%; p=0.07). Three domains were substantially more frequently represented in the 'implementation group' as compared to the 'control group' and were even assessed in all trials of the implementation group: 'physical function' (100% vs 42%; $p \leq 0.001$), 'peripheral joints/entheses' (100% vs 33%; $p \leq 0.001$) and 'fatigue' (100% vs 0%; $p \leq 0.001$). Four domains also show a high level of usage in the 'implementation group' but were already high in the 'control group': 'pain' (100% vs 92%), 'spinal mobility' (81% vs 92%), 'spinal stiffness' (100% vs 92%) and 'acute phase reactants' (96% vs 83%).

Instruments

A number of instruments had a low usage in the trials of both the 'implementation group' and 'control group': 'pain night' (42% vs 33%) and 'joint count' (42% vs 33%). With respect to the instrument 'joint count' the number of joints assessed was very different ranging from 22 to 70 joints. Three instruments were substantially more frequently reported in the 'implementation' vs the 'control group': 'BASFI' (100% vs 8%), 'BASMI' (54% vs 0%) and 'CRP' (92% vs 59%). The domain 'pain global' was frequently used in both groups (100% vs 92%). Concerning 'radiographic progression', two instruments -'mSASSS' and 'BASRI'- were used, but were only reported in 'implementation trials'. The instruments 'MASES' and 'Berlin', both for the domain 'peripheral joint/entheses', were evaluated only after 2001. Although the most commonly selected instrument

to evaluate 'physical function' in the 'implementation group' was the 'BASFI', in many trials more than one instrument was used to evaluate this domain.

Table 3 Implementation of ASAS/OMERACT Core Outcome Set (DC-ART) and specific instruments in each domain in trials evaluating interventions with DMARDs, biological drugs or glucocorticoids.

DC-ART	Control group (before 2001) (n = 12)[1]		Implementation group (after 2001) (n= 26)[2]		
Assessment	**Performed** (n, %)	**Reported separately** (n, %)	**Performed** (n, %)	**Reported separately** (n, %)	**p value** ¶
Physical function	**5 (41.7)**	-	**26 (100)**	-	**< 0.001**
BASFI	1 (8.3)	-	26 (100)	-	
Dougados-FI	4 (33.3)	-	1 (3.8)	-	
HAQ	1 (8.3)	-	4 (15.4)	-	
Pain*	**11 (91.7)**	**11 (91.7)**	**26 (100)**	**19 (73.1)**	**0.3**
Night	4 (33.3)	-	11 (42.3)	-	
Global*	11 (91.7)	11 (91.7)	26 (100)	19 (73.1)	
Spinal mobility**	**11 (91.7)**	**11 (91.7)**	**21 (80.8)**	**21 (80.8)**	**0.4**
BASMI	0	-	14 (53.8)	-	
Cervical rotation**	2 (16.7)	2 (16.7)	14 (53.8)	4 (15.4)	
Lateral spinal flexion**	0	0	15 (57.7)	5 (19.2)	
Schober	7 (58.3)	-	8 (30.8)	-	
Modified Schober**	4 (33.3)	4 (33.3)	18 (69.2)	5 (19.2)	
Intermalleolar distance**	0	0	14 (53.8)	4 (15.4)	
Tragus to wall distance**	0	0	15 (57.7)	5 (19.2)	
Occiput to wall distance	4 (33.3)	-	7 (26.9)	-	
Chest expansion	10 (83.3)	-	12 (46.2)	-	
Spinal stiffness*	**11 (91.7)**	**11 (91.7)**	**26 (100)**	**15 (57.7)**	**0.1**
Patient global assessment	**8 (66.7)**	-	**16 (61.4)**	**-**	**0.8**
Peripheral Joints/entheses*	**4 (33.3)**	**4 (33.3)**	**26 (100)**	**14 (53.8)**	**< 0.001**
Joint count	4 (33.3)	-	11 (42.3)	-	
MASES	0	-	4 (15.4)	-	
Berlin Index	0	-	1 (3.8)	-	
Acute phase reactants	**10 (83.3)**	-	**25 (96.2)**	**-**	**0.2**
CRP	7 (58.3)	-	24 (92.3)	-	
ESR	10 (83.3)	-	13 (50.0)	-	
Spine radiograph	**0**	**-**	**6 (23.1)**	-	**0.07**
mSASSS	0	-	4 (15.4)	-	
BASRI	0	-	3 (11.5)	-	
Fatigue*	**0**	**0**	**26 (100)**	**7 (26.9)**	**< 0.001**

¶ p values are for comparison between assessment performed in control and implementation group

[1]Intervention in these studies: DMARDs (10) and glucocorticoids (2)

[2]Intervention in these studies: DMARDs (3) and biological drugs (23)

***** If BASDAI was reported, we considered the following domains (fatigue, pain, stiffness and peripheral joint/entheses) were performed although these were not separately reported.** If BASMI was reported, we considered this domain (spinal mobility) and the following instruments (lateral spinal flexion, tragus to wall distance, modified Schober, Intermalleolar distance and cervical rotation) were performed although these were not separately reported. DC-ART, disease controlling anti-rheumatic therapy; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, linear definition of the Bath Ankylosing Spondylitis Metrology Index, CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; MASES, Maastricht Ankylosing Spondylitis Enthesis; BASRI, Bath Ankylosing Spondylitis Radiology Index

RCTs evaluating NSAIDs, physical therapy and miscellaneous interventions

Domains and instruments

These results on implementation in RCTs evaluating NSAIDs, physical therapy and miscellaneous interventions are shown in table 4. The domain 'patient's global assessment' showed a low percentage of usage in the 'implementation group', and even lower than in the trials of the 'control group' (36% vs 51%). 'Physical function' and 'fatigue' were significantly more frequently used in the trials of the 'implementation group' as compared to the 'control group': (92% vs 23%; p=<0.001 and 84% vs 17%; p<0.001), respectively, whereas the domain 'pain' had a high representation in the trials of both groups (96% vs 89%).

Regarding the instruments, we found that 'Dougados FI' and 'night pain' had a rather low representation in trials of both groups: (8% vs 9%) and (20% vs 44%) respectively. The representation of 'BASFI' (88% vs 14%) and 'BASMI' (52% vs 0%), however, improved significantly in 'implementation trials', while 'global pain' (96% vs 86%) remained at a high level in both groups.

Table 4 Implementation of ASAS/OMERACT Core Outcome Set (SMARD) and specific instruments in each domain in trials evaluating interventions other than DMARD, biological drugs or glucocorticoids

SMARD	Control group (before 2001) (n = 36)[1]		Implementation group (after 2001) (n= 25)[2]		
Assessment	Performed (n, %)	Reported separately (n, %)	Performed (n, %)	Reported separately (n, %)	p value ¶
Physical function	**8 (22.9)**	-	**23 (92.0)**	-	**< 0.001**
BASFI	5 (14.3)	-	22 (88.0)	-	
Dougados-FI	3 (8.6)	-	2 (8.0)	-	
HAQ	3 (8.6)	-	0	-	
Pain*	**32 (88.8)**	**30 (85.7)**	**24 (96.0)**	**15 (60.0)**	**0.3**
Night	16 (44.4)	-	5 (20.0)	-	
Global*	30 (85.8)	29 (82.9)	24 (96.0)	15 (60.0)	
Spinal mobility**	**28 (77.7)**	**27 (77.1)**	**23 (92.0)**	**23 (92.0)**	**0.1**
BASMI	0	-	13 (52.0)	-	
Cervical rotation**	2 (5.7)	2 (5.7)	13 (52.0)	6 (24.0)	
Lateral spinal flexion**	5 (14.3)	5 (14.3)	14 (56.0)	7 (28.0)	
Schober	21 (58.3)	-	5 (20.0)	-	
Modified Schober**	3 (8.6)	3 (8.6)	18 (72.0)	10 (40.0)	
Intermalleolar distance**	2 (5.7)	2 (5.7)	14 (56.0)	7 (28.0)	
Tragus to wall distance**	1 (2.9)	1 (2.9)	14 (56.0)	6 (24.0)	
Occiput to wall distance	12 (34.3)	-	7 (28.0)	-	
Chest expansion	24 (66.6)	-	17 (68.0)	-	
Spinal stiffness*	**25 (71.5)**	**24 (68.6)**	**22 (88.0)**	**11 (50.0)**	**0.1**
Patient global assessment	**18 (51.4)**	-	**9 (36.0)**	-	**0.2**
Fatigue*	**6 (17.1)**	**4 (11.4)**	**21 (84.0)**	**6 (24.0)**	**0.001**

¶ p values are for comparison between assessment performed in control and implementation group

[1]Intervention in these studies: NSAIDs (25), physical therapy (5) and miscellaneous (6)

[2]Intervention in these studies: NSAIDs (4), physical therapy (13), balneotherapy (5) and miscellaneous (3)

***** If BASDAI was reported, we considered the following domains (fatigue, pain, stiffness and peripheral joint/enthuses) was performed although it was not separately reported.

** If BASMI was reported, we considered this domain (spinal mobility) and the following instruments (lateral spinal flexion, tragus to wall distance, modified Schober, Intermalleolar distance and cervical rotation) were performed although these were not separately reported.

Evolution of usage of domains and instruments over time

In order to illustrate the evolution of the representation of domains and instruments, figures 2a and 2b were constructed. An increasing usage of domains and instruments was found over time. Looking at the results, the increased usage was primarily attributable to the advent of RCTs testing biological drugs shortly after the year 2001. We did not find an important increase in usage of domains over time in RCTs with NSAIDs, DMARDs or miscellaneous interventions, but the number of ASAS core-set instruments per RCT increased not only in biological drugs RCTs but also in RCTs with miscellaneous interventions.

Figure 2a Dot plot illustrating the number of ASAS core set domains per trial according to the date of publication and type of intervention. Miscellaneous interventions in this context, include physical therapy and other kind of treatments. Glucocorticoids are included in DMARDs interventions. All studies (n=99).

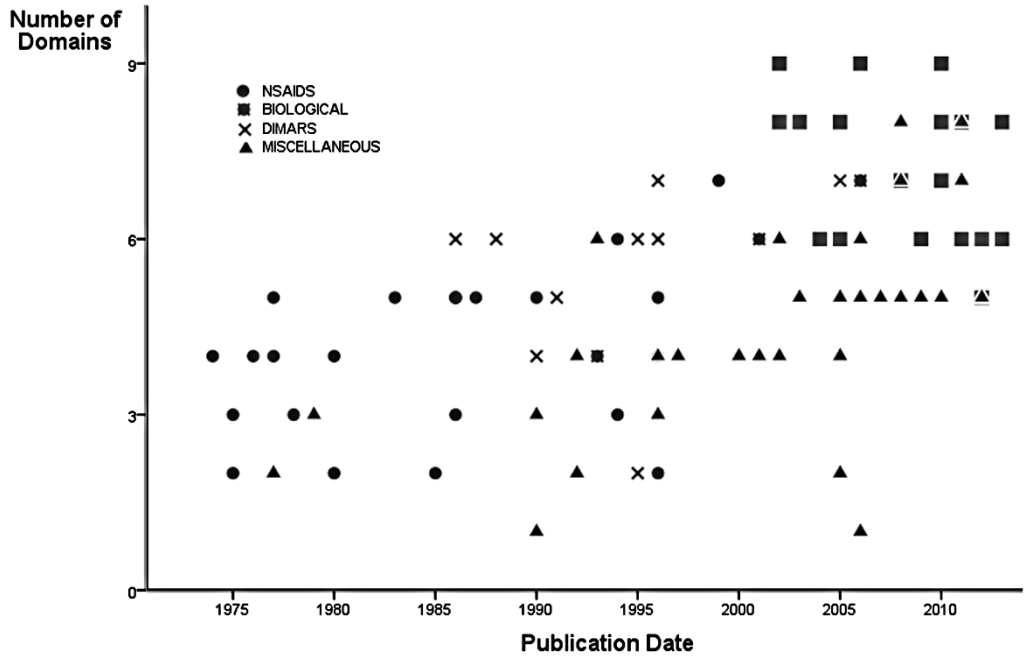
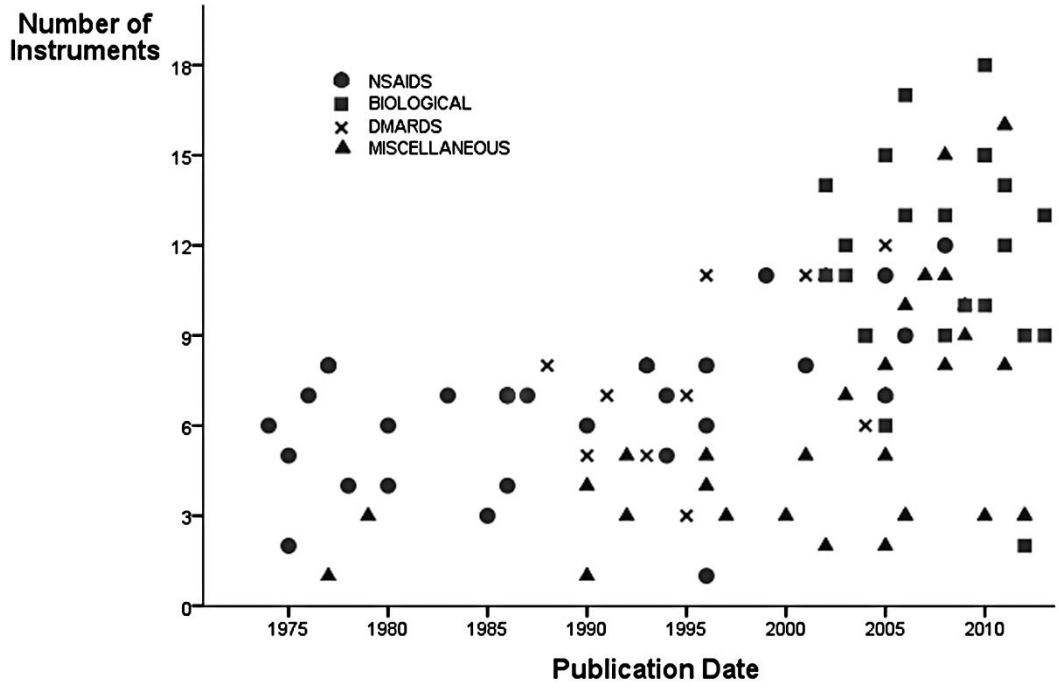


Figure 2b Dot-plot illustrating the number of ASAS core-set instruments per trial according to the date of publication and type of intervention. Miscellaneous interventions in this context, include physical therapy and other kind of treatments. Glucocorticoids are included in DMARDs interventions. All studies (n=99).



ASAS-endorsed response criteria and other outcomes

Since the ASAS response criteria and partial remission criteria were published in 2001 (ASAS 20 and ASAS partial remission criteria) and in 2004 (ASAS 40 and ASAS 5/6), only studies published two years after those dates (n=45 and n=33 respectively) were included in the analyses (in this context only trials from the 'implementation group' were investigated). ASAS 20 response criteria were reported in 40% of the trials (18 out of 45 trials), ASAS 40 in 45% (15 out of 33) of the trials, ASAS 5/6 in 30% (10 out of 33) and ASAS partial remission in 22% (10 out of 45). The reported percentages for each response criteria are different mainly due to the publication date and the implementation time. The number of trials reporting the response criteria are not the same -e.g. ASAS 20 (45 trials) and ASAS 40 (30 trials).

In Table 5, the ASAS response criteria are presented according to type of intervention. A high level of usage was found in trials with biological drugs (ASAS 20 (73%), ASAS 40 (93%), ASAS partial remission (53%) and ASAS 5/6 (60%). BASDAI 50 was reported as response measure only in implementation trials (25%; n= 13).

Table 5 Usage of ASAS response criteria according to trial intervention

Intervention (%)	ASAS 20*	ASAS partial remission*	ASAS 40**	ASAS 5/6**
NSAID	2/4 (50)	0/4 (0)	0/2 (0)	0/2 (0)
Biological drugs	14/19 (73.3)	10/19 (52.6)	14/15 (93.3)	9/15 (60)
Physical therapy	1/13 (7.7)	0/13 (0)	1/11 (9.1)	1/11 (9.1)
Miscellaneous	1/2 (50)	0/2 (0)	0/2 (0)	0/2 (0)

Trials included since 2004* and 2006** according to publication date of respective response criteria

DISCUSSION

This study confirms the implementation of the ASAS/OMERACT core set in randomized clinical trials after the original publication. A substantial improvement in the utilization of ASAS-endorsed domains and to a lesser extent of ASAS-endorsed instruments overtime is evident. Additionally, an increasing number of RCTs has reported a full or nearly full spectrum of ASAS-core domains, which was observed across all interventions. Overall, the utilization of the DC-ART core set is very good and better than that of the SMARD core set.

The domains ‘physical function’, ‘peripheral joint/entheses’, ‘fatigue’ and ‘spine radiograph’ improved substantially over time. ´Physical function’ is considered an important outcome measure for the evaluation of disease evolution and additionally is a domain relevant to the patient, and is reported by a high proportion of studies (92%). Moreover, ‘BASFI’ included by ASAS as the preferred instrument, is far more often used as a method for the evaluation of ‘physical function’ (88%).

A similar trend of utilization was observed with the domain 'spine radiograph'. With the expectation that there would be a positive effect by treatment on structural damage, it stimulated the inclusion of this domain in more recent trials. The domains 'acute phase reactants', 'pain', 'spinal mobility' and 'spinal stiffness' were already frequently used before the publication of the core sets and this has remained unchanged. The only domain that did not show an increased usage over time is 'patient global assessment' (61% for DC-ART and 36% for SMARD core set).

Regarding the specific instruments to measure each domain there is clearly more homogeneity, as non-endorsed instruments that were used frequently in the past are not used so often anymore after the introduction of the core set. Nevertheless, the overall level of implementation of specific instruments still leaves room for further improvement, especially for the SMARD core set.

A remarkable improvement in the usage of domains and instruments is attributable to RCTs with biological treatments, intended for drug registration purposes. These RCTs are usually of very high methodological quality, and trial planning teams that were responsible for the choice of primary and secondary outcome measures have scrutinized the literature to search for the best set of instruments. In this context the ASAS core-set as such, may have contributed to the performance of these trials, to a more transparent drug registration process and to a better acceptance of new treatments in the field.

The ASAS response and partial remission criteria are intended for use in the evaluation of drug treatment. Therefore, it could be expected that the best implementation is seen in trials evaluating biological therapies, and this is most obvious with regard to the use of the ASAS40 and ASAS5/6,

which were developed to assess relatively better responses, as could be expected to occur in efficient drugs such as biological drugs.

As a possible limitation of our analysis is that the time period of two years after the publication as a cut-off point between the two groups of trials, is an arbitrary choice and may not be sufficient to assess the implementation properly. Indeed we have found that there is a further increase in implementation over the years. A strength of this study is that a primary and very comprehensive search of the entire literature was conducted specifically aiming at the population of interest.

All domains and instruments that have been used in the trials should be reported. Interestingly we have found that sometimes domains and instruments were used but not reported separately. For example, the domain 'fatigue', which is included in the 'BASDAI', as well as specific instruments included in the BASMI, were not always reported separately. There might be several explanations for this. A trivial one is space constraint, but online appendices may resolve this problem. Another possibility is that authors only report positive results. Most likely, however, authors may not understand the purpose of core sets: Reporting outcomes of a trial in a homogeneous manner, with the aim to avoid publication bias and the possibility to compare measures across trials.

In conclusion, this study provides evidence for the utilization of the ASAS/OMERACT core-set in RCTs of both DC-ART and SMARD, especially to the use of the domains and to a lesser extent to the use of specific instruments. However, there is room for improvement, aiming at reporting the complete core-set and their instruments.

APPENDIX 1

Systematic search strategy terms: MEDLINE / EMBASE

Population: Ankylosing Spondylitis, Spondyloarthritis

1. Bechterew Disease
2. Bechterew's Disease
3. Bechterews Disease
4. Ankylosing Spondyloarthritis
5. Ankylosing Spondyloarthritides
6. Spondyloarthritides, Ankylosing
7. Spondyloarthritis, Ankylosing
8. Rheumatoid Spondylitis
9. Spondylitis, Rheumatoid
10. Spondylarthritis Ankylopoietica
11. Ankylosing Spondylarthritis
12. Ankylosing Spondylarthritides
13. Spondylarthritides, Ankylosing
14. Spondylarthritis, Ankylosing
15. Ankylosing Spondylitis
16. Marie-Struempell Disease
17. Marie Struempell Disease

Study design: publication type
1. Randomized controlled trial

Language restriction:
1. English
2. French
3. German
4. Spanish
5. Dutch
6. Portuguese

APPENDIX 2

References of all papers included in the systematic literature review for a detail revision (127)

1. Sieper J et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013 Jun;72(6):815-22.

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8

Summary and Discussion

SUMARY AND DISCUSSION

The studies presented in this thesis cover many aspects related to Spondyloarthritis (SpA) in Colombia. The following topics were addressed. First, the analyses and performance of the different SpA classification criteria and the factors important in the decision of the rheumatologist to order an MRI or HLA-B27 test in the diagnostic work-up of SpA in the context of the clinical rheumatology setting. Second, a better insight was obtained with regard to the presence of comorbidities and risk factors of patients with SpA. This included also a case-control study to evaluate the relationship between periodontitis and SpA. Third, the translation and cross-cultural adaptation to Spanish of the ASAS-HI was performed. Finally, the implementation of the domains and instruments of the ASAS core set in clinical trials have been evaluated.

In this final chapter, we summarize the main findings of the studies included in this thesis. In addition, we will discuss the potential unmet needs in the field of rheumatology in Colombia and we propose a research agenda for the upcoming years.

In the first study presented in this thesis, the performance of the various classification criteria developed for SpA (ESSG, Amor and ASAS criteria) was tested in a clinical practice cohort of patients in Colombia. Patients with a clinical diagnosis of SpA (defined as the reference standard) were analysed for the various characteristics included in these classification criteria in **chapter 2**. In this cohort, the ASAS criteria were most sensitive in classifying patients having SpA in comparison to ESSG and Amor criteria. Even, the addition of MRI did not substantially increase the classification rate of ESSG and Amor criteria. Similar findings with regard to the validity of the ASAS criteria using the clinical diagnosis as reference have been reported in the European SPACE cohort [1]. In both studies, a substantial rate of concordance with regard to the different criteria sets was observed.

Considering the marked heterogeneity of axial SpA, this agreement may suggest that the core characteristics of SpA are captured by all criteria. Many Colombian rheumatologists establish a diagnosis of SpA based on these typical clinical characteristics. However, a bias with regard to additional testing of MRI and HLA-B27 was present in this study. These additional tests were mainly performed based on clinical indication only, especially in those patients with the highest probability of having SpA and in those patients with an uncertain diagnosis. The fact that MRI and HLA-B27 was not available for all patients may have hampered the comparison of the various criteria sets, especially those sets that include one or both tests. Recently, a systematic literature review has confirmed the good performance and the validity of the various ASAS SpA criteria as tested against the rheumatologist's diagnosis [2]. However, in contrast to these validation studies we found a higher prevalence of peripheral involvement in Colombian patients. This finding has been consistently observed in Latin America for peripheral arthritis as well as for enthesitis [3]. Moreover, the frequency of HLA-B27 in our cohort was also rather low in contrast to data reported in other regions including Europe [4]. Differences in the prevalence of HLA-B27 in Colombian population, which has a wide geographic and ethnic variation, may explain these findings. Despite these differences in prevalence of peripheral symptoms and HLA-B27 in our Colombian dataset, the performance of the ASAS SpA criteria is very similar to the published data.

While in clinical practice rheumatologists do not perform MRI or HLA-B27 testing in all patients with a suspicion of SpA, they do require these tests in those patients with the highest probability of having SpA and in those patients in which clinical symptoms fall short to diagnose but suspicion remains. Because of cost, waiting time for MRI and feasibility issues, these tests cannot be performed in all patients suspected of having SpA. In **chapter 3**, using the same data as employed in the analyses of the study in **chapter 2**, we have investigated the patient's characteristics

associated with a clinical decision to order a SI-MRI and/or HLA-B27 testing in the diagnostic work-up of SpA. We found that the presence of inflammatory back pain (IBP), enthesitis, the number of symptoms at presentation and uveitis increased the likelihood of ordering MRI and/or HLA-B27 testing. These clinical clues are important, because the presence of these manifestations increase the pre-test probability of axial SpA and therefore the finding of a positive test may significantly contribute to confirming a diagnosis while finding a negative test may help ruling out the disease. This is an appropriate manner of increasing the diagnostic efficiency and optimizing the use of resources. A recent study from the ESPERANZA cohort has investigated the utility of SpA features associated with a higher likelihood of a positive SI-MRI or a positive HLA-B27 in patients with chronic back pain [5]. They found that IBP according to the ASAS definition plus alternating buttock pain or IBP according to Calin criteria plus awakening in the second half of the night predicted the presence of finding sacroiliitis on MRI. Our findings assigned IBP as a determinant for ordering SI-MRI. Together, these studies confirm that the presence of IBP not only evokes an SI-MRI-order, but also that this behaviour is rational in that the likelihood of a positive result will increase. Our results suggest that clinical reasoning indeed follows the principles of Bayesian theory and that it helps rheumatologists to improve efficiency of these tests. Moreover, the efficiency of MRI improves when the patients are optimally selected, which relies on training about the appropriate use of SpA features [6].

In the study presented in **chapter 4** we have performed a comparative study with the general population on data from Latin American patients (including Colombia) from the multinational Assessment of SpondyloArthritis international Society of COMOrbidities in SpA (ASAS-COMOSPA) study [7]. The most common comorbidities and risk factors were arterial hypertension (AHT), hypercholesterolemia, osteoporosis and gastrointestinal ulcer. The prevalence of AHT (including

data from Colombia and Mexico) was increased compared to the general population resulting in a standardized risk ratio (SRR) of 1.5 (95% CI 1.0 to 2.1). Many studies have reported a higher prevalence of AHT in AS [8, 9], which may reflect the detrimental effects that chronic inflammation may have on endothelial function and acceleration of atherosclerosis. The common use of NSAIDS in this cohort of patients may also play a role, even though NSAID-use was associated with less mortality in a study by Bakland et al [10]. In addition, the prevalence of tuberculosis (TB) was importantly higher than expected from the general population in LA, resulting in an SRR of 10.3 (95% CI 6.1 to 17.8). Uncontrolled and chronic inflammation may predispose to TB, in addition to the risk that patients receiving immunosuppressive treatments such as corticosteroids [11] and TNF-inhibitors already have [12]. The prevalence and risk of malignancies in comparison to the general population was not significantly increased. Although these findings could not be extrapolated to the whole region (patients came from the three Latin American countries that participated in the ASAS-COMOSPA study), this is one of the first efforts to evaluate comorbidities associated to SpA in Latin America. Our findings described in **chapter 4** may have implications for daily clinical practice with regard to rheumatologist's health assessments, prevention and treatment planning.

While clinical studies have pointed towards a relationship between chronic periodontitis and rheumatoid arthritis [13], it was unclear if SpA patients have a higher frequency of periodontitis. A case-control study evaluating the clinical, serological and microbiological periodontal condition in a group of patients with SpA is described in **chapter 5**. We did not find a positive association between SpA and periodontitis and we found even a lower prevalence of periodontitis and less severe periodontitis in comparison to matched-healthy controls. The explanation of these findings is unclear, however, from a physiopathological point of view, it is obvious that the citrullination [14] of proteins is a biochemical process that likely is not relevant in the pathogenesis of SpA.

The ASAS Health Index has been developed as a composite index based on the International Classification of Functioning (ICF) to measure the impact of SpA on patients' lives [15]. The translation and cross-cultural adaptation of the English version of ASAS-HI was performed and presented in **chapter 6** using a standardized operating procedure in Colombian patients with SpA [16]. The adapted version of the ASAS-HI maintained the good psychometric properties of the original English-language version of the questionnaire in terms of reliability, sensitivity to change, construct validity and discriminative capacity regarding thresholds of disease activity. This validated ASAS-HI in Spanish-speaking patients with SpA may be used in clinical practice and research studies. This instrument is complementary to other validated tools that assess disease activity, physical function and quality of life in Spanish-language, thus completing the toolkit for the assessment of Colombian patients with SpA [17] [18].

The definition of core sets and the choice of appropriate instruments are relevant in order to incorporate important elements from both the patient's and the physician's perspective in clinical research. This is particularly important when considering AS and SpA with regard to treatment comparisons and when considering which measures and outcomes to report in clinical trials [19]. In order to evaluate the implementation of the ASAS/OMERACT core sets [20], a systematic literature review has been performed to analyse and compare the usage of domains, instruments and ASAS response criteria. The findings are presented in **chapter 7** and confirm the implementation of the core set in randomized clinical trials after the original publication of the core set in 1999. Overall, the utilization of the disease controlling anti-rheumatic therapy (DC-ART) core set was better than that of the symptom modifying anti-rheumatic drugs SMARD core set. With respect to the ASAS response criteria, as expected, the best implementation was seen evaluating biological therapies.

However, there is still room for improvement, aiming at reporting the complete core set and its instruments.

Implications of this thesis and future perspectives

The studies described in this thesis cover relevant aspects of the landscape of Spondyloarthritis in Colombia in terms of the performance of classification criteria, the behaviour of rheumatologists considering additional testing, as well as comorbidities and risk factors and assessment of health status. In a field in which clinical research has been dominated by Europe, this thesis may improves the body of knowledge of a condition that has not been properly investigated in Colombia.

The confirmation of the validity of the ASAS SpA classification criteria in a South American population supports the good performance of these criteria when tested against the rheumatologist´s diagnosis. It also supports the inclusion of patients fulfilling these criteria in research studies, ensuring that the patient population is comparable to other regions of the world. This may bring research efforts in Colombia at a higher level. For clinical practice, the appropriate selection of additional testing in patients suspected of having SpA based on clinical clues is relevant. This pre-selection of patients based on pure clinical reasoning, may help to optimize the distribution of health resources and avoid increasing costs of diagnostic tests. This is relevant, especially in case of limited resources, which is still the reality in all Latin American countries. We strongly believe, that clinical decision making based on Bayesian principles, rather than using classification criteria inappropriately, will lead to an improvement of quality of care in clinical practice. A monitoring strategy of patients with SpA focusing on treating or avoiding comorbidities that we have established here as relevant, may guide rheumatologists to optimize treatment in their SpA patients. Moreover, the availability of an adapted version of the ASAS-HI will lead to

further exploring the health status and functioning of Colombian patients with SpA. Equally important, we have demonstrated that there is no relationship between SpA and periodontitis. This finding may not necessarily have clinical implications will help in providing a better understanding of the pathophysiology of SpA, since it contrasts with that of RA in terms of the importance of citrullination.

Still, we may face many challenges and unmet needs that will require to be addressed in order to better understand the burden and the severity of SpA in Colombia and similarly in Latin America. National epidemiological studies including representative samples across the countries, may give better insight into the prevalence of SpA that of HLA-B27 in our population. The implementation and validation of early referral strategies may improve the identification of patients in primary care. This type of interventions may help to reduce the time of delay of the diagnosis, which has not been estimated yet. With regard to evaluating the contribution of MRI to establishing a diagnosis, extensive training is warranted in collaboration with radiologists.

Future improvements of knowledge will lead to increased awareness and earlier diagnosis of SpA. Collaborative efforts aiming at promoting clinical and basic research in patients with SpA will provide a platform that consolidates this area of research in Latin America. In this regard, the design and implementation of a registry for collecting information by a standardized protocol will contribute to this purpose.

In summary, in this thesis we have presented and discussed many topics in relation to the field of spondyloarthritis in Colombia. Definite progress has been made, but we have to keep moving so that our patients in Colombia will be better served.

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9

Samenvatting en Discussie

SAMENVATTING EN DISCUSSIE

Dit proefschrift gaat over de ziekte spondyloarthritis (SpA), in het bijzonder in het Zuid-Amerikaanse land Colombia. SpA is een chronische reumatische ziekte waarbij ontsteking van de bekkengewrichten (de SI-gewrichten), de wervelkolom en de perifere gewrichten (zoals knieën, enkels) kan optreden. Tegenwoordig wordt de ziekte onderverdeeld in axiale SpA (axSpA) (met name klachten als gevolg van ontsteking van de bekkengewrichten en de wervelkolom) en perifere SpA (pSpA) (met name klachten als gevolg van ontstekingen in- of rond de perifere gewrichten). Vrijwel alle patiënten met SpA hebben last van pijn en stijfheid in rug en/of gewrichten. Een scala aan andere manifestaties kan optreden bij axSpA en pSpA, zoals chronische darmontsteking, oogontsteking (uveitis) of psoriasis (huidziekte). De oorzaak van SpA is onbekend, maar SpA is deels erfelijk bepaald via het gen dat is genaamd HLA-B27[1]. De ontsteking van de SI-gewrichten en de wervelkolom kan zichtbaar worden gemaakt op een zogenaamde MRI-scan[2]. Het bepalen van HLA-B27 in het bloed en het beoordelen van een MRI-scan van de SI-gewrichten zijn tegenwoordig dan ook hoekstenen van de diagnostiek van SpA. Er bestaan zogenaamde classificatiecriteria voor axSpA en pSpA, die de ziekte en al haar manifestaties beschrijven. De meest recente criteria zijn de ASAS[3]-criteria uit 2009. Met nadruk zij gesteld dat deze criteria niet dienen om de diagnose SpA te stellen, maar veeleer om patiënten met SpA in wetenschappelijk onderzoek op te nemen.

In dit proefschrift is onderzocht of deze ASAS-classificatiecriteria ook 'goed werken' bij patiënten met de diagnose SpA in Colombia. Dat was niet op voorhand zeker, omdat de diagnose SpA wereldwijd verschillend wordt gesteld. Dit heeft te maken met de opvattingen van reumatologen over de ziekte SpA, met de technische mogelijkheden die reumatologen hebben om een diagnose te stellen (niet iedereen heeft bijvoorbeeld de mogelijkheid om een MRI te vervaardigen, of om op HLA-B27 te testen) en met de mate van toegankelijkheid van reumatologische zorg (kosten, aantal reumatologen).

In *hoofdstuk 2* is een groep patiënten beschreven die volgens de Colombiaanse reumatologen SpA hebben (diagnose). Er is gekeken in welke mate deze SpA-patiënten voldeden aan de diverse classificatiecriteria. De voornoemde ASAS-criteria bleken meer patiënten met de diagnose SpA op te pikken (waren sensitiever) dan de oudere ESSG[4]- en Amor[5]

classificatiecriteria (die van vóór het MRI tijdperk zijn). Zelfs als MRI werd toegevoegd als criterium aan de ESSG en Amor criteria bleken deze toch niet even goed te zijn als de ASAS-criteria. Twee opmerkelijke zaken werden gevonden. Ten eerste maakten Colombiaanse reumatologen (waarschijnlijke gedwongen uit kostenoverwegingen) spaarzaam gebruik van HLA-B27-test en MRI-scan. Zij deden dit alleen bij gerede twijfel over de diagnose SpA, maar niet standaard bij alle patiënten. Ten tweede bleek dat een verhoudingsgewijs groot deel van de SpA-patiënten in Colombia perifere SpA had. In Europa zien we juist meer axiale SpA. Dit is een bekend gegeven in landen in Latijns-Amerika, dat ook in andere studies werd gevonden.

In *hoofdstuk 3* is nader onderzocht bij welke patiënten met SpA HLA-B27 en MRI werd aangevraagd. Het bleek dat vooral bij patiënten met voor SpA typische rugpijnklachten (de zogenaamde inflammatoire rugpijn) MRI en HLA-B27 werden aangevraagd, maar verder ook bij patiënten met de voor SpA kenmerkende oogontsteking (uveitis anterior) en bij hen die meerdere symptomen van SpA hadden. Feitelijk betekent dit dat Colombiaanse reumatologen op doelmatige wijze gebruik maken van beperkte (dure) diagnostische hulpmiddelen, hetgeen de kosten van de zorg voor patiënt en samenleving in belangrijke mate beperkt.

In *hoofdstuk 4* wordt een onderzoek beschreven naar het vóórkomen van andere ziekten (co-morbiditeiten) bij patiënten met SpA in Latijns-Amerika, namelijk Colombia, Mexico en Argentinië. Hiertoe werd gebruik gemaakt van Latijns-Amerikaanse data uit het wereldwijde ASAS-COMOSPA[6] onderzoek, waarbij co-morbiditeiten bij SpA zijn gemeten. Door te vergelijken met bevolkingsgegevens uit Colombia en Mexico werd aannemelijk gemaakt dat met name hoge bloeddruk frequent optreedt bij SpA patiënten in deze landen. Mogelijk komt dit door chronische ontsteking die van invloed is op de vaatwand en op het ontwikkelen van atherosclerose. Maar het kan ook zijn dat de onstekingsremmers die gebruikt worden bij SpA (de zogenaamde NSAIDs[7]) een bloeddruk verhogend effect hebben. Voorts werd gevonden dat SpA patiënten in Latijns-Amerika vaker dan verwacht lijden aan de infectieziekte tuberculose. Dit kan het gevolg zijn van de chronische ontsteking die de afweer onderdrukt, of wellicht door afweer-onderdrukkende medicijnen (prednison, TNF-blokkers[8]). Kwaadaardige ziekten kwamen daarentegen niet vaker voor bij SpA- patiënten. De resultaten

van dit onderzoek geven de reumatologen in Zuid-Amerika een handvat om patiënten met SpA beter en gerichter te monitoren.

In *hoofdstuk 5* wordt een geheel andere weg ingeslagen. Periodontitis is een bacteriële ontsteking van de weefsels rondom de tanden. Periodontitis kan leiden tot chronische aantasting van het kaakbot en verlies van tanden en kiezen. Maar tegenwoordig wordt ook gedacht dat periodontitis het ontstaan van reumatische ziekten (en hart- en vaatziekten) kan bevorderen. Voor de ziekte reumatoïde artritis (RA) is dit aannemelijk gemaakt. De ziekte SpA heeft enkele overeenkomsten met RA (naast vele verschillen) en we kennen de oorzaak van SpA niet. De hypothese die ten grondslag lag aan het onderzoek beschreven in *hoofdstuk 5* was dat er een samenhang bestaat tussen SpA en periodontitis. Om die hypothese te toetsen werden Colombiaanse patiënten met SpA uitgebreid periodontologisch onderzocht, en werden de bevindingen vergeleken met die van Colombianen zonder SpA. Hoewel periodontitis zeer frequent werd gevonden in de Colombiaanse bevolking werd er absoluut geen samenhang gevonden tussen periodontitis en SpA, zodat aannemelijk kon worden gemaakt dat –althans in Colombia – periodontitis géén risicofactor voor het ontstaan van SpA is, dit in tegenstelling tot RA, waar die samenhang overigens bescheiden is.

In *hoofdstuk 6* werd vervolgens het proces beschreven van de vertaling van de Engelstalige ASAS-Health Index, een vragenlijst om het algemeen functioneren van SpA- patiënten te meten, naar het in Colombia gebruikelijke Spaans. Zo'n vertaling lijkt op het eerste gezicht een eenvoudige procedure maar dat is het niet. Immers, de betekenis van verschillende woorden en uitdrukkingen zijn sterk cultureel bepaald, en niet één-op-één vanuit het Engels naar het Spaans te vertalen zonder dat de precieze betekenis van de woorden verloren gaat. Voor dergelijke 'transculturele adaptaties' van vragenlijsten is een gestandaardiseerd proces ontwikkeld, dat werd doorlopen om een voor Colombia gevalideerde vertaling van de ASAS-Health Index te verkrijgen.

In *Hoofdstuk 7*, tenslotte, worden de resultaten beschreven van een systematisch literatuuronderzoek naar het gebruik van zogenaamde 'core-set variabelen' in trials bij patiënten met SpA. Core-set variabelen zijn variabelen die door de experts van ASAS en OMERACT[9] zijn aangemerkt als een minimum om de uitkomst van wetenschappelijk

onderzoek bij patiënten met SpA te meten. Deze core-set werd in 1999 vastgesteld, en is nog steeds actueel. Voor dit literatuuronderzoek waren wij vooral benieuwd of de core-set variabelen ook daadwerkelijk vaker werden gemeten en gerapporteerd ná 1999 dan vóór 1999. Dit is belangrijk omdat uniformiteit van metingen bijdraagt aan onderlinge vergelijkbaarheid van onderzoeksresultaten. Wij konden inderdaad aantonen dat het meten en rapporteren van core-set variabelen na 1999 beduidend was verbeterd, met name bij de grote trials met biologische geneesmiddelen na 2002. Er is echter nog steeds ruimte voor een betere implementatie van de core-set.

Nawoord

De ziekte SpA is tot dusver weinig onderzocht in Colombia en andere landen in Latijns Amerika. Het is zeer waarschijnlijk dat deze aandoening, die zich bij voorkeur manifesteert op jongvolwassen leeftijd, een grote impact heeft op patiënten en samenleving. Door een achterstand in kennis bij gezondheidswerkers op het gebied van de diagnose en behandeling van SpA, door een gebrekkige fysieke en financiële toegankelijkheid tot de gezondheidszorg, en waarschijnlijk ook door een tekort aan ervaren reumatologen, is die impact van de ziekte in landen als Colombia wellicht groter dan in ontwikkelde landen. Dit proefschrift zou er aan kunnen bijdragen dat er in landen als Colombia meer aandacht ontstaat voor herkenning van SpA, voor de voordelen van vroegdiagnostiek en voor optimale behandeling. Hiertoe is het van groot belang dat gestructureerd wetenschappelijk patiëntgebonden onderzoek wordt geïnitieerd. Mede onder invloed van het onderzoek verricht in de context van dit proefschrift, staat zulk patiëntgebonden onderzoek in Colombia nu stevig in de steigers.

Voetnoten

1. HLA-B27: Human Leucocyte Antigen B27, de belangrijkste erfelijke factor die geassocieerd is met de ziekte SpA en kan worden gemeten in het bloed van patiënten verdacht voor SpA.
2. MRI-scan: Magnetic Resonance Imaging-scan, een vorm van beeldvormend onderzoek waarbij ontsteking en beschadiging van beenmerg en bot kan worden opgespoord bij patiënten verdacht van SpA.
3. ASAS: Assessment in SpondyloArthritis international Society. ASAS is een wereldwijde organisatie van klinische wetenschappers op het gebied van de ziekte SpA.

4. ESSG: European Spondylarthropathy Study Group. De groep die de eerste classificatiecriteria voor SpA heeft ontwikkeld (1999)

5. Amor: Naar de Franse reumatoloog Bernard Amor die een alternatieve set van classificatiecriteria heeft ontwikkeld.

6. COMOSPA: Comorbidities in Spondyloarthritis, een patiëntonderzoek van ASAS.

7. NSAIDs: Non Steroidal Anti-Inflammatory Drugs: Ontstekingsremmers met een pijnstillend effect, toegepast bij reumatische aandoeningen.

8. TNF-blokkers: Tumor Necrosis Factor-blokkerende geneesmiddelen. Biologische geneesmiddelen die het effect van dit ontstekingseiwit remmen en worden toepast bij reumatische ontstekingsziekten

9. OMERACT: Outcome Measures in Rheumatology Clinical Trials. OMERACT is een wereldwijde organisatie van onderzoekers op het gebied van het meten van de uitkomst van reumatische ziekten in klinische trials, in de breedste zin van het woord.

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Curriculum Vitae

Wilson Bautista was born on the 19th of September 1980 in Duitama, Colombia. He studied Medicine at the Universidad Nacional de Colombia and obtained his medical degree in December 2003. He obtained his degree in Internal Medicine at the Universidad Militar Nueva Granada in the Hospital Militar Central in Bogotá, Colombia in April 2010. Later, he started his training in Rheumatology at the Department of Rheumatology in the same University. During the second year of Rheumatology training he was awarded a fellowship by the Assessment of SpondyloArthritis international Society. He moved to The Netherlands in 2011 and worked as a research fellow at the Rheumatology Department of the Leiden University Medical Center (LUMC) in Leiden. This rotation at the LUMC was instrumental for him to choose an academic career and perform clinical research. As a result of the research fellowship this thesis was started and performed at the LUMC. The thesis focused on many aspects related to spondyloarthritis in Colombia. He obtained his MSc in Rheumatology in Colombia in 2012. He is currently Professor of Medicine and Rheumatology at the School of Medicine in the Universidad Militar Nueva Granada and also is working as consultant rheumatologist in the Arthritis Clinic at Organización Sanitas Internacional in Bogotá, Colombia.

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