

Current Controversies in Spondyloarthritis: SPARTAN

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Current Controversies in Spondyloarthritis: SPARTAN

MICHAEL WEISMAN, THOMAS J. LEARCH, XENOFON BARALIAKOS, VINOD CHANDRAN, DAFNA D. GLADMAN, SIBA P. RAYCHAUDHURI, HUJI XU, EDUARDO COLLANTES-ESTÉVEZ, JANITZIA VÁZQUEZ-MELLADO, PHILIP J. MEASE, JOACHIM SIEPER, ATUL A. DEODHAR, ROBERT A. COLBERT, and DANIEL O. CLEGG, for the SPARTAN Group

ABSTRACT. The Spondyloarthritis Research and Therapy Network (SPARTAN), founded in 2003 to promote research, education, and treatment of ankylosing spondylitis (AS) and related forms of spondyloarthritis (SpA), held its 7th Annual Research and Education Meeting in July 2009 in Houston, Texas. Current controversies in SpA discussed during the meeting included an update on the epidemiology of AS, axial SpA, and inflammatory back pain; the adequacy of the mSASS to assess radiographic involvement; the helpfulness of magnetic resonance imaging in assessing disease progression; the reliability of metrology in assessing damage; and whether biologic agents alter the course of AS. Presentations also were made on psoriasis in the SCID mouse model; the challenges and opportunities of SpA in China; a discussion of the special needs in managing SpA in Ibero-America, and the SPARK Survey in Europe and North America. (*J Rheumatol* 2010; 37:2617–23; doi:3899/jrheum.100890)

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The Spondyloarthritis Research and Therapy Network (SPARTAN; www.spartangroup.org) was founded in 2003 by a group of North American clinicians and researchers who meet yearly to promote research, education, and treatment of spondyloarthritis (SpA)^{1,2,3,4}.

Current controversies in SpA were discussed at the 7th annual research meeting in July 2009 in Houston, Texas, USA; discussions included an update on the epidemiology

of AS, axial SpA, and inflammatory back pain (IBP); adequacy of the modified Stoke Ankylosing Spondylitis Spine Score (mSASS) to assess radiographic involvement; the helpfulness of magnetic resonance imaging (MRI) in assessing disease progression; the reliability of metrology in assessing damage; and whether biologic agents alter the course of ankylosing spondylitis (AS). Presentations also were made on psoriasis in the SCID mouse model; the challenges and opportunities of SpA in China; a discussion of the special needs in managing SpA in Ibero-America, and the SPARK Survey in Europe and North America. An educational pre-meeting conference was specifically designed for rheumatology fellows.

Epidemiology of AS, Axial SpA, and Inflammatory Back Pain

Michael Weisman, MD (Cedars-Sinai Medical Center, Los Angeles, CA, USA) began with a review of the published literature addressing the current prevalence of AS, SpA, and IBP in the United States⁵, France^{6,7}, and Lithuania⁸. He pointed out that variable methodologies have been employed to estimate prevalence of different diseases in different countries and a true comparison between prevalence of AS and rheumatoid arthritis (RA) is not possible. He also presented the latest SpA classification criteria, which have been finalized and validated by the Assessment of Spondyloarthritis International Society (ASAS)⁹. These new criteria establish the importance of clinical features (primarily IBP) as well as MRI evidence of inflammation. Dr.

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Weisman then discussed the status of the case ascertainment tool for AS, which has been developed and validated to assess the role of IBP as a diagnostic precursor for AS if employed in a chronic back pain population¹⁰.

Dr. Weisman then provided an update of the National Health and Nutritional Examination Survey (NHANES) 2009-2010 IBP/SpA epidemiology survey, whose goals, design, and data collection were outlined at the SPARTAN meeting in 2008⁴. He emphasized the role of genetic testing and the importance of IBP in the survey questions, saying that a case definition of IBP may be more predictive of AS than unvalidated clinical criteria.

Dr. Weisman next discussed the role of genetic markers for diagnosis and population screening. He described early results from a recent Australo-Anglo-American Spondylitis Consortium (TASC) genome-wide association study, in which 2053 Australian, British, and North American Caucasian AS cases fulfilling the modified New York Criteria were ethnically matched to control genotypes¹¹. This group identified (in addition to HLA-B27) the new genetic markers ERAP1 (endoplasmic reticulum aminopeptidase; also known as ARTS1), IL23R, and regions on chromosomes 2p15 and 21q22. Likelihood ratios computed by logistic regression were used to determine the post-test probability of AS given the pre-test probability and new genetic findings, and compared these to MRI scanning, assuming a sensitivity and specificity of 90% for this modality¹². He agreed with the TASC group that genetic markers warrant consideration for both clinical and population screening for risk of AS compared to MRI assessment and clinical assessments, with the caveat that background genetic heterogeneity has to be considered when applying these methods for epidemiology studies to the population at large.

Imaging: Does the mSASS Adequately Assess Radiographic Involvement?

Thomas J. Leach, MD (Cedars-Sinai Medical Center, Los Angeles, CA, USA) reviewed the 2 radiographic scoring methods for AS, the modified Stoke Ankylosing Spondylitis Spine Score (mSASS) and the Bath Ankylosing Spondylitis Radiology Index (BASRI). Although both methods assess the lateral cervical and lateral lumbar spine, only the BASRI assesses the lumbar spine on an anterior-posterior (AP) projection. Syndesmophytes and fusion may be present on the AP view of the lumbar spine, but not on the lateral view, leading to underdiagnosis of disease on the mSASS system. Neither method assesses special projections [e.g., flexion/extension views of spine, Ferguson or oblique views of sacroiliac (SI) joints].

Dr. Leach reviewed the scoring systems for each method, presenting case radiographs with their relative mSASS and BASRI scores to demonstrate conflicts between the 2 systems. He emphasized the many characteristics that do not get scored, including atlantoaxial subluxation, cran-

iocervical fusion, ischial erosions, and pubic symphysis fusion. Additionally, many features of the disease may initially be normal on radiographs but abnormal on advanced imaging — particularly MRI. This includes early inflammatory changes [sacroiliitis, discitis (Andersson lesion), Romanus lesions, hip effusion/synovitis]. Using radiographs, computed tomography, and MRI from individual cases, he demonstrated how important these characteristics may be to early diagnosis of AS. In particular, hip disease is found frequently in AS and is associated clinically and radiographically with more severe spinal disease.

Dr. Leach concluded that the mSASS was developed for research purposes during the pre-TNF era and that now we need more detailed assessment criteria that assess early disease states and both active and inactive disease. MRI is more sensitive for early diagnosis and pathology and also can be used to follow patient disease progression or remission.

Imaging: How Helpful Is MRI in Assessing Disease Progression in AS?

Xenofon Baraliakos, MD (Rheumazentrum Ruhrgebiet Herne, Ruhr-University Bochum, Germany) emphasized the importance of early-stage diagnosis of AS patients, given that the mean delay in diagnosing AS is 7–9 years¹³. He cited results published recently by ASAS, in which imaging plays a crucial role, since presence of early stages of sacroiliitis observed on MRI in combination with other features of SpA may lead to early diagnosis, with a sensitivity of 66.2% and a specificity of 84.4%⁹. Moreover, MRI can provide new insight in disease-related pathology: there appears to be a good correlation between MRI and the histology of SI joint biopsies, showing T cell infiltrates in SI joints of patients with AS¹⁴.

Dr. Baraliakos presented results from several studies using anti-tumor necrosis factor- α (TNF- α) therapies for AS^{15,16,17,18,19}: Changes in MRI scores do not correlate to baseline inflammatory activity¹⁶ or to change in clinical parameters²⁰. However, baseline MRI activity can be used as a predictive parameter for response to treatment with TNF-blockers in AS²¹. He presented results from recent studies showing that response to treatment appears to improve when MRI are used to diagnose AS at an earlier stage of disease^{22,23}. Finally, he discussed the value of MRI for understanding chronic disease progression, specifically in assessing the thoracic spine and understanding new bone formation²⁴.

What Is the Reliability of Metrology in Assessing AS Damage?

Vinod Chandran, MBBS, MD, DM, on behalf of Dafna D. Gladman, MD, FRCPC (University of Toronto, Ontario, Canada), first defined metrology as it applies to AS, with photographs to demonstrate measurement of hyperkyphosis

(occiput-to-wall and tragus-to-wall distances), cervical spine (rotation)²⁵, thoracic spine (chest expansion)²⁵, and lumbar spine (lateral and forward flexion — including finger-to-floor distance, modified Schober's test, and 3 x 10 cm segment contraction)^{25,26}. He then discussed how these measures are included in one or both of 2 metrology composite measures: the Bath AS Metrology Index (BASMI)²⁷ and the Edmonton AS Metrology Index (EASMI)²⁸. Discussion followed on these measures and on the composite index included in the ASAS core set.

Dr. Chandran next discussed the reliability of metrology, as outlined by OMERACT (Outcome Measures in Rheumatology Clinical Trials)²⁹. He first presented a chart summarizing general inter- and intraobserver reliability³⁰, followed by specific reliability data from the INSPIRE study (INternational SPondyloarthritis Interobserver Reliability Exercise)³¹. He concluded that cervical rotation, lateral spinal flexion, intermalleolar distance, and chest expansion are the most responsive metrology measurements in clinical trials, and that hyperkyphosis is better measured using occiput-to-wall rather than tragus-to-wall assessments.

Also discussed was the assessment of damage in AS²⁵ and the relationship of metrology to damage. Metrology correlates with damage mainly in late disease³². It has been shown that some metrologic measures are sensitive to change with effective therapy; however, further assessment is needed of metrology's relationship with radiographic change measures^{30,33}.

SCID Mouse Model of Psoriasis

Siba P. Raychaudhuri, MD (University of California, Davis, CA, USA) emphasized that the SCID mouse model is a unique tool for drug development of autoreactive T cell and Th17 cell-mediated autoimmune diseases such as psoriasis, where xenogenic transplantation models allow investigation of a disease process in a microenvironment resembling its natural milieu^{34,35}. In this model, biopsy samples are collected from patients with chronic plaque psoriasis and grafted onto BALB/cByJSmn-Prkdcscid/J SCID mice. Histologic and immunologic features of psoriasis appear to be maintained in transplanted grafts of psoriatic tissue for 16–20 weeks^{34,36}, which may allow investigators to develop novel drugs for this disease.

Although several molecules have been identified over the lifetime of transplanted plaques on SCID mice [p38 MAPK, STAT3, ICAM, CXCR3, fractalkine, interleukin 8 (IL-8), CD3, CD4, CD8, HLA-DR, CD40, OX 40R, CD80, CD86, K16, Ki67, substance P, nerve growth factor (NGF), and NGF receptor], it appears that costimulatory molecules have a critical role for T cell activation³⁴. A principal signal is delivered by the engagement of CD28 on T cells with CD80 (B7-1) and CD86 (B7-2) on antigen-presenting cells. Langerhans cells, dermal dendrocytes, and the activated T

cells express CD80 and CD86, the ligands of the costimulatory molecules.

Because upregulation of CD80/CD86 in psoriatic lesions suggests a critical role for the CD28/B7 costimulatory system in the pathogenesis of psoriasis, inhibition of the CD28 and CD80/CD86 interaction may restrict the inflammatory processes of psoriasis. In a double-blind, placebo-controlled study, transplanted psoriatic plaques on SCID mice were treated with CTLA4IgG, a natural inhibitor of CD28/B7 costimulatory signals; cyclosporine was used as a positive control, and untreated plaques were negative controls. CTLA4IgG-treated plaques significantly improved following 4 weeks of therapy; similar improvement was observed in the cyclosporine group, whereas the untreated plaques did not improve³⁴.

Recent animal studies revealed critical roles of IL-17 in the development of autoimmune diseases. IL-17 is produced by Th17 cells, a unique subset of helper T cells. After extensive *in vivo/in vitro* studies, it was possible to identify and determine the phenotypes and functional significance of Th17 cells in PsA³⁵, where Th17 cells were significantly higher in psoriatic synovial tissue and psoriatic plaques than in controls. Identification of Th17 cells in skin and synovium of psoriatic tissue suggests its possible pathologic role in the psoriatic disease process and may offer a rational therapeutic target. The SCID mouse model of psoriasis continues to be used to explore treatment of autoimmune diseases by targeting Th17 cells with IL-17 and IL-17R antibody.

Spondyloarthritis in China: Challenges and Opportunities

Huji Xu, MD, PhD (Shanghai Changzheng Hospital, Second Military Medical University, Shanghai, China) reminded the group that China is still a developing country with limited and imbalanced health resources. China has 1.3 billion people and only 2.3 million doctors, 20% of the world's population and only 2% of its health resources. Eighty percent of China's doctors work in major cities, but even in Shanghai the number of rheumatologists is limited. Several associations are active in China: the Chinese Rheumatology Association is an academic organization that primarily educates the public about rheumatic diseases; the Chinese Rheumatologists' Association trains and licenses Chinese rheumatologists; and the Bone and Joint Decade Arthritis Taskforce, under the auspices of the Chinese Ministry of Health, promotes public awareness of arthritis, using media coverage, guidelines for physicians, and journal articles. The Chinese Rheumatology Workforce surveyed 2216 rheumatologists in 29 provinces between October and December 2007.

In a recent review, 241,169 individuals were involved in 38 surveys of the epidemiology of rheumatic disease in China³⁷, which showed a prevalence of AS of 0.2%–0.54%, or potentially 3.9 million people. AS is more frequent in

men than in women (10:1 ratio), onset before age 40 years is common, and genetic factors (HLA-B27) play an important role³⁸. Physicians have promoted cheaper therapies [nonsteroidal antiinflammatory drugs (NSAID)], but would prefer to use traditional [disease modifying antirheumatic drugs (DMARD)] or biologic therapies (anti-TNF- α), if they were more affordable. Most (58%) Chinese patients are willing to pay additional out-of-pocket expenses for therapies if they are covered by reimbursement drug lists. Because of the high number of eligible patients with AS and their access to care and relatively high income, there is a large potential market for biologics in China.

Much research in SpA in China is supported by the government (National Natural Science Foundation; Ministry of Science and Technology). Dr. Xu presented some recent results, including association with the IL-1 gene complex, HLA-B27 subtypes in AS patients and controls, and the susceptibility genes in Chinese Han people with AS^{39,40,41}. He concluded, however, that more funding is needed, as well as national and international collaboration, for rheumatology research, education, and treatment to succeed in China.

Special Needs for Managing SpA in Ibero-America

Eduardo Collantes-Estévez, MD, PhD (University Hospital of Córdoba, Spain) and Janitzia Vázquez-Mellado, MD, PhD (Hospital General de Mexico, Mexico City, Mexico) defined Ibero-America (IBA) for the group — Spain, Portugal, and Latin America (Mexico and Central and South America) — which represents a total of 700 million people with a similar culture, language, and religion, but with many socioeconomic disparities (e.g., access to healthcare and social security). He also introduced the RESPONDIA study (Registro de Espondiloartritis de Ibero-América), in which about 100 rheumatologists from 11 countries are participating in an observational, cross-sectional, multicenter, and multinational study of 2044 patients with SpA⁴².

Using standard measures for classifying SpA [Bath AS Disease Activity Index, Bath AS Functional index (BASFI), BASRI, etc.], preliminary data from RESPONDIA indicate that 51% of patients have AS, with smaller numbers with psoriatic arthritis (PsA; 18%), juvenile SpA (8%), undifferentiated SpA (uSpA; 21%), and other forms of SpA (< 3%); 30% of patients have axial disease and 36% have chronic hip pain. Typical patients are male (67%), 44 years old, with disease duration of 13 years; 63% are HLA-B27-positive. About 52% of patients with AS have severe AS at diagnosis, as defined by association with HLA-B27, more structural damage, and more axial and less peripheral involvement. Patients in RESPONDIA follow a standard treatment pathway, from NSAID to DMARD to biologics; however, socioeconomic differences have been detected.

Dr. Vázquez-Mellado showed that in IBA, the pattern of SpA appears influenced by the socioeconomic level. Patients in the low socioeconomic level are younger at dis-

ease onset and have tarsitis more often; they also have limited cervical mobility, higher AS Quality of Life and BASFI scores, and are diagnosed more frequently with uSpA. They are treated less often with anti-TNF agents.

Prof. Collantes-Estévez discussed another analysis, in which 466 AS patients from RESPONDIA were compared with 1045 patients from REGISPONSER (Registro Español de Espondiloartritis, Spain) and 847 patients from ASPECT (AS Patients Epidemiological Cross-sectional, a Belgium database). Latin American patients generally have higher BASFI scores, more hip involvement, and more enthesitis and arthritis, compared with European patients, but lower HLA-B27 association and less IBD. Hip involvement associated with impaired functioning is reflected in higher overall BASFI scores. Early onset of disease, both axial and enthesitis, are associated with hip replacement surgery in AS⁴³.

Dr. Vázquez-Mellado emphasized that these results represent patients attended by rheumatologists; patients in rural areas have access only to general practitioners. It is imperative that rheumatologists share their information so that early diagnosis and treatment can be optimized for all patients.

The SPARK Survey: SpA in Rheumatology Practices in Europe and North America

Philip Mease, MD (Swedish Medical Center and University of Washington, Seattle, WA, USA) reminded the group of the objectives of SPARK (SPondyloarthritis: Assessment of CuRrent Epidemiology, Management, and Knowledge), an international survey conducted between July and September 2008, designed to determine the epidemiology (prevalence of SpA patients under rheumatologist care; relative prevalence of SpA subtypes), diagnosis (relative sensitivity of different classification criteria), and management trends of SpA (NSAID, DMARD, biologics; imaging modalities; differences in functional impairment) in rheumatology practices in 9 countries in Europe and North America. He shared examples of the 3 questionnaires used for the SPARK survey (2 for physicians; 1 for patients), which involved nearly 500 rheumatologists and 2700 patients. He stressed the limitations of the survey: it selected for SpA-sensitive clinicians, did not standardize SpA category definitions before the survey, many initial surveys were “guestimates” of diagnosis frequencies, and the survey was done before revised SpA classification criteria were introduced.

Dr. Mease then reviewed initial data on the variability of RA versus SpA in global rheumatology practices, sharing country-by-country data on physician practice and relative size of patient subgroups (RA vs SpA; SpA subtypes)⁴⁴. Percentages of RA and SpA patients observed in some countries were nearly equal; however, in the average practice in the US, 60% were RA patients compared with 40% SpA patients. Percentages of various subsets of SpA also varied from country to country. In the USA, PsA comprised 36.4%

of the SpA population, AS 22.7%, uSpA 17.7%, reactive SpA 11.7%, and IBD-related SpA 11.5%.

He also shared initial data from a substudy of patients with psoriatic spondylitis or AS with psoriasis⁴⁵. The SPARK survey collected information on SpA diseases (classified using the modified New York criteria for AS)⁴⁶ as well as psoriatic disease, using the Classification Criteria for Psoriatic Arthritis (CASPAR)⁴⁷. Participants in this substudy included 168 physicians from Europe and Canada and 1669 of their patients, all of whom had ≥ 1 diagnosis of SpA (63.5% SpA, 23.5% PsA). Three hundred forty-four patients with AS or PsA or both had axial involvement and psoriasis, and about half these patients fulfilled both the modified NY criteria and the CASPAR criteria regardless of the presence or absence of peripheral arthritis⁴⁵.

Dr. Mease briefly discussed the relationship between SpA and work productivity. Of the 968 patients (68%) in SPARK who were employed at the time of the survey, 28.7% of patients had overall work impairment and 36.7% had activity impairment; percentages were similar across SpA subgroups⁴⁸.

Dr. Mease noted that more SPARK questionnaires were planned of the combined European and North American databases, including analyses of treatment patterns, patient satisfaction with therapy, and additional aspects of disease epidemiology.

Do Biologic Agents Alter the Course of AS?

Joachim Sieper, MD (Rheumatology, Charité, Campus Benjamin Franklin, Berlin, Germany) reviewed 3 separate, well known studies of TNF- α agents in AS, in which infliximab, etanercept, and adalimumab showed remarkably similar efficacy in clinical response measures (ASAS 40)^{49,50,51}. However, he stressed that inflammation and new bone formation might be uncoupled once structural damage has been established. He showed several instances of sacroiliitis, with and without bony changes, and reviewed recent data where infliximab and etanercept did not inhibit new bone formation in the spine after 2 years^{52,53}.

Dr. Sieper proposed a sequence of structural damage in AS⁵⁴, comparing the process with RA⁵⁵. Although erosive bone destruction is the result of inflammation in both diseases (fluctuating in AS; persistent in RA), further inflammation in AS after replacement by repair tissue in AS results in osteoproliferation, specifically syndesmophyte formation^{56,57}. Dr. Sieper reviewed recent data showing that the negative effect of sclerostin on osteocytes may be antagonistic to new bone formation⁵⁸. Challenges that researchers face include how to better define where and when structural damage starts (inflammation, fibrous tissue, fatty deposition?), and to identify how early antiinflammatory treatment should begin to prevent chronic structural damage in patients with AS.

Highlights of Fellows Meeting

On the day before the general meeting, 30 rheumatology fellows from training programs in the US and Canada participated in a one-day review course on SpA. Topics included “Overview of Genetics of Rheumatic Disease in the 21st Century” (Peter Gregersen, MD); “Classification and Epidemiology” (M. Asim Khan, MD); “Overview of Pathogenesis” (Robert Inman, MD); “Assessing Functional Capacity and Outcomes in SpA” (Michael Ward, MD); “Clinical Features of SpA” (James Rosenbaum, MD); “Clinical Features in PsA” (Christopher Ritchlin, MD); “Imaging” (Thomas Learch, MD); and “An Overview of Treatment” (Drs. Atul Deodhar and Philip Mease).

Future Plans of SPARTAN

SPARTAN will continue to support clinical research projects and a Web-based learning module for trainees. Our next Annual Research and Education meeting will be held July 23–24, 2010, in Houston, Texas (see www.spartangroup.org).

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