Current Controversies in Spondyloarthritis: SPARTAN

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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.

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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 States[5], France[6,7], and Lithuania[8]. 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.

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 population[10].

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 2008[4]. 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 genotypes[11]. 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 modality[12]. 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. Learch, 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. Learch 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, craniocervical 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. Learch 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 years[13]. 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 AS[14].

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 activity[16] or to change in clinical parameters[20]. However, baseline MRI activity can be used as a predictive parameter for response to treatment with TNF-blockers in AS[21]. 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 formation[24].

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 reliability[30], 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 AS[25] and the relationship of metrology to damage. Metrology correlates with damage mainly in late disease[32]. 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 activation[34]. 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 improve[34].

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 PsA[35], 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 China[37], 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 role[38]. 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 SpA[42].

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 disease 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 enthesial, are associated with hip replacement surgery in AS[43].

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 psoriasis[45]. 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 arthritis[45].

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 subgroups[48].

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 AS[54], comparing the process with RA[55]. 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 formation[58]. 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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REFERENCES

1. Ward MM, Bruckel J, Colbert R, Deodhar A, Emerson C, Genant H, et al. Summary of the 2005 Annual Research and Education Meeting of the Spondyloarthritis Research and Therapy Network (SPARTAN). J Rheumatol 2005;33:978-82.
2. Khan MA, Clegg DO, Deodhar AA, Gabriel S, Gaston JS, Hirsch R, et al. 2006 annual research and education meeting of the Spondyloarthritis Research and Therapy Network (SPARTAN). J Rheumatol 2007;34:1118-24.
3. Colbert RA, Deodhar AA, Khan MA, Lories RJ, Maksymowych WP, Reveille JD, et al. 2007 annual research and education meeting of the Spondyloarthritis Research and Therapy Network (SPARTAN). J Rheumatol 2008;35:1398-402.
4. Colbert RA, Deodhar AA, Fox D, Gravallese EM, Khan MA, McGonagle D, et al. Entheses and bones in spondyloarthritis: 2008 Annual Research and Education Meeting of the Spondyloarthritis Research and Therapy Network (SPARTAN). J Rheumatol 2009;36:1527-31.
5. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum 2008;58:15-25.
6. Saraux A, Guillemin F, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, et al. Prevalence of spondyloarthropathies in France: 2001. Ann Rheum Dis 2005;64:1431-5.
7. Guillemin F, Saraux A, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, et al. Prevalence of rheumatoid arthritis in France: 2001. Ann Rheum Dis 2005;64:1427-30.
8. Adomaviciute D, Pileckyte M, Baranauskaite A, Morvan J, Dadoniene J, Guillemin F. Prevalence survey of rheumatoid arthritis and spondyloarthropathy in Lithuania. Scand J Rheumatol 2008;37:113-9.
9. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for

axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777-83.
10. Weisman MH, Chen L, Clegg DO, Davis JC, Jr, Dubois RW, Prete PE, et al. Development and validation of a case ascertainment tool for ankylosing spondylitis. Arthritis Care Res 2010;62:19-27.
11. Barrett JC, Lee JC, Lees CW, Prescott NJ, Anderson CA, Phillips A, et al. Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. Nat Genet 2009;41:1330-4.
12. Evans D, Reveille JD, Weisman MH, Stone MA, Ward MM, Savage L, et al. Diagnostic capacity of genetic tests in ankylosing spondylitis can exceed MRI scanning [abstract]. Arthritis Rheum 2008;58 Suppl:S904.
13. Feldtkeller E, Bruckel J, Khan MA. Scientific contributions of ankylosing spondylitis patient advocacy groups. Curr Opin Rheumatol 2000;12:239-47.
14. Bollow M, Fischer T, Reisshauer H, Backhaus M, Sieper J, Hamm B, et al. Quantitative analyses of sacroiliac biopsies in spondyloarthropathies: T cells and macrophages predominate in early and active sacroiliitis — cellularity correlates with the degree of enhancement detected by magnetic resonance imaging. Ann Rheum Dis 2000;59:135-40.
15. Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002;359:1187-93.
16. Braun J, Landewe R, Hermann KG, Han J, Yan S, Williamson P, et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum 2006;54:1646-52.
17. Sieper J, Baraliakos X, Listing J, Brandt J, Haibel H, Rudwaleit M, et al. Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 yrs of treatment with the anti-tumour necrosis factor agent infliximab. Rheumatology 2005;44:1525-30.
18. Baraliakos X, Davis J, Tsuji W, Braun J. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. Arthritis Rheum 2005;52:1216-23.
19. Rudwaleit M, Baraliakos X, Listing J, Brandt J, Sieper J, Braun J. Magnetic resonance imaging of the spine and the sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloarthritis during treatment with etanercept. Ann Rheum Dis 2005;64:1305-10.
20. Braun J, Baraliakos X, Golder W, Brandt J, Rudwaleit M, Listing J, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis Rheum 2003;48:1126-36.
21. Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. Ann Rheum Dis 2008;67:1276-81.
22. Barkham N, Keen HI, Coates LC, O'Connor P, Hensor E, Fraser AD, et al. Clinical and imaging efficacy of infliximab in HLA-B27-positive patients with magnetic resonance imaging-determined early sacroiliitis. Arthritis Rheum 2009;60:946-54.
23. Haibel H, Baraliakos X, Rudwaleit M, Listing J, Wong R, Kupper H, et al. Adalimumab reduces inflammation in the sacroiliac joints of patients with active spondyloarthritis without radiographic sacroiliitis — results of a placebo-controlled, double-blind clinical trial through 52 weeks [abstract]. Ann Rheum Dis 2009;68 Suppl 3:628.
24. Baraliakos X, Listing J, Rudwaleit M, Sieper J, Braun J. Development of a radiographic scoring tool for ankylosing spondylitis only based on bone formation: addition of the thoracic spine improves sensitivity to change. Arthritis Rheum 2009; 61:764-71.
25. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68 Suppl 2:ii1-44.
26. Miller MH, Lee P, Smythe HA, Goldsmith CH. Measurements of spinal mobility in the sagittal plane: new skin contraction technique compared with established methods. J Rheumatol 1984;11:507-11.
27. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21:1694-8.
28. Maksymowych WP, Mallon C, Richardson R, Conner-Spady B, Jauregui E, Chung C, et al. Development and validation of the Edmonton Ankylosing Spondylitis Metrology Index. Arthritis Rheum 2006;55:575-82.
29. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol 1998;25:198-9.
30. Davis JC Jr, Gladman DD. Spinal mobility measures in spondyloarthritis: application of the OMERACT filter. J Rheumatol 2007;34:666-70.
31. Gladman DD, Inman RD, Cook RJ, van der Heijde D, Landewe RB, Braun J, et al. International spondyloarthritis interobserver reliability exercise — the INSPIRE study: I. Assessment of spinal measures. J Rheumatol 2007;34:1733-9.
32. Machado P, van der Heijde D, Braun J, Hermann K, Hsu B, Baker D, et al. Both clinical disease activity and spinal mobility contribute to physical function in patients with ankylosing spondylitis [abstract]. Ann Rheum Dis 2009;68 Suppl 3:646.
33. Chandran V, O'Shea FD, Schentag CT, Inman RD, Gladman DD. Relationship between spinal mobility and radiographic damage in ankylosing spondylitis and psoriatic spondylitis: a comparative analysis. J Rheumatol 2007;34:2463-5.
34. Raychaudhuri SP, Kundu-Raychaudhuri S, Tamura K, Masunaga T, Kubo K, Hanaoka K, et al. FR255734, a humanized, Fc-silent, anti-CD28 antibody, improves psoriasis in the SCID mouse-psoriasis xenograft model. J Invest Dermatol 2008;128:1969-76.
35. Raychaudhuri SP, Raychaudhuri SK, Genovese MC. Phenotypic and functional features of Th-17 cells in psoriasis and psoriatic arthritis [abstract]. Arthritis Rheum 2008;58 Suppl:S352.
36. Raychaudhuri SP, Jiang WY, Raychaudhuri SK. Revisiting the Koebner phenomenon: role of NGF and its receptor system in the pathogenesis of psoriasis. Am J Pathol 2008;172:961-71.
37. Zeng QY, Chen R, Darmawan J, Xiao ZY, Chen SB, Wigley R, et al. Rheumatic diseases in China. Arthritis Res Ther 2008;10:R17.
38. Liao Z, Pan Y, Huang J, Huang F, Chi W, Zhang K, et al. An epidemiological survey of low back pain and axial spondyloarthritis in a Chinese Han population. Scand J Rheumatol 2009:1-5.
39. Sims AM, Timms AE, Bruges-Armas J, Burgos-Vargas R, Chou CT, Doan T, et al. Prospective meta-analysis of interleukin 1 gene complex polymorphisms confirms associations with ankylosing spondylitis. Ann Rheum Dis 2008;67:1305-9.
40. Liu Y, Jiang L, Cai Q, Danoy P, Barnardo MC, Brown MA, et al. Predominant association of HLA-B*2704 with ankylosing spondylitis in Chinese Han patients. Tissue Antigens 2010;75:61-4. Epub 2009 Oct 4.
41. Davidson SI, Wu X, Liu Y, Wei M, Danoy PA, Thomas G, et al. Association of ERAP1, but not IL23R, with ankylosing spondylitis in a Han Chinese population. Arthritis Rheum 2009;60:3263-8.
42. Vazquez-Mellado V, Sampaio-Barros P, Berman A, Smith D, Brown MA, White E, et al. The pattern of ankylosing spondylitis (AS) in

Ibero-America (IBA): the RESPONDIA group report II [abstract]. Clin Exp Rheumatol 2008;26:742.
43. Vander Cruyssen B, Munoz-Gomariz E, Font P, Mulero J, de Vlam K, Boonen A, et al. Hip involvement in ankylosing spondylitis: epidemiology and risk factors associated with hip replacement surgery. Rheumatology 2010;49:73-81.
44. Dougados M, Combescure C, Sieper J, Mease P, Lavie F, Pangan A, et al. Intercountry variability of the relative percentage of rheumatoid arthritis versus spondyloarthritis in rheumatologic daily practice [abstract]. Ann Rheum Dis 2009;68 Suppl:531.
45. van der Heijde D, Pangan AL, Mease P, Sieper J, Combescure C, Dougados M. Psoriatic spondylitis or ankylosing spondylitis with psoriasis: insights from the SPARK international survey [abstract]. Ann Rheum Dis 2009;68 Suppl:347.
46. Moll JM, Wright V. New York clinical criteria for ankylosing spondylitis. A statistical evaluation. Ann Rheum Dis 1973; 32:354-63.
47. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.
48. Gooch K, Dougados M, van der Heijde D, Mease P, Sieper J, Pangan AL, et al. Relationship between spondyloarthropathies and impaired work productivity [abstract]. Ann Rheum Dis 2009;68 Suppl:356.
49. van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005; 52:582-91.
50. Davis JC, van der Heijde DM, Braun J, Dougados M, Cush J, Clegg D, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. Ann Rheum Dis 2005;64:1557-62.
51. van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:2136-46.
52. van der Heijde D, Landewe R, Baraliakos X, Houben H, van Tubergen A, Williamson P, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum 2008;58:3063-70.
53. van der Heijde D, Landewe R, Einstein S, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum 2008;58:1324-31.
54. Appel H, Sieper J. Spondyloarthritis at the crossroads of imaging, pathology, and structural damage in the era of biologics. Curr Rheumatol Rep 2008;10:356-63.
55. Sieper J, Appel H, Braun J, Rudwaleit M. Critical appraisal of assessment of structural damage in ankylosing spondylitis: implications for treatment outcomes. Arthritis Rheum 2008; 58:649-56.
56. Maksymowych WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Ostergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. Arthritis Rheum 2009;60:93-102.
57. Appel H, Kuhne M, Spiekermann S, Kohler D, Zacher J, Stein H, et al. Immunohistochemical analysis of hip arthritis in ankylosing spondylitis: evaluation of the bone-cartilage interface and subchondral bone marrow. Arthritis Rheum 2006;54:1805-13.
58. Appel H, Ruiz-Heiland G, Listing J, Zwerina J, Herrmann M, Mueller R, et al. Altered skeletal expression of sclerostin and its link to radiographic progression in ankylosing spondylitis. Arthritis Rheum 2009;60:3257-62.