Meeting Report

Summary of the 2005 Annual Research and Education Meeting of the Spondyloarthritis Research and Therapy Network (SPARTAN)

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The mission of the Spondyloarthritis Research and Therapy Network (SPARTAN; www.spartangroup.org) is to promote research, education, and treatment of spondyloarthritis (SpA). At the Annual Research and Education meeting held in August 2005 in San Francisco, USA, SPARTAN members were updated on new research in the genetics, pathogenesis, imaging modalities, and clinical features of SpA. In breakout sessions, the group discussed important issues concerning (1) the epidemiology of SpA, (2) disease classification and heterogeneity among pediatric patients with SpA, and (3) treatment guidelines.

The SPARTAN was founded in 2003 by a group of North American clinicians and researchers interested in promoting research, education, and treatment of SpA. SPARTAN works closely with the Spondylitis Association of America (SAA) to promote its mission. SPARTAN has produced and disseminated United States-specific modifications of the Assessments in Ankylosing Spondylitis (ASAS) guidelines for the use of anti-tumor necrosis factor (anti-TNF) therapy in AS (June 2003), and has held 3 annual research meetings, the most recent in August 2005 in San Francisco, California. The program was organized into general sessions on basic and clinical science, and breakout sessions on epidemiology, pediatrics, and treatments for AS. Highlights of the program included summaries of recent research developments, review and commentary on planned research projects, and discussions of treatment controversies. An important new feature of this meeting was an education pre-meeting conference specifically designed for rheumatology fellows, along with the opportunity for fellows to present their research.

Update from Spondylitis Association of America (SAA)

Christopher Emerson, MA, (SAA) introduced the SAA as the nation's leading patient advocacy organization for ankylosing spondylitis (AS) and related diseases. He emphasized that a primary goal of the SAA is to advance the search for a cure for these diseases, specifically by providing patient populations for research, supporting collaboration among researchers, and funding and facilitating research (e.g., the AS Life Impact Study, the AS Family Genetic Project, development of a screening tool for AS). A second goal is to provide information needed by patients, their families, and caregivers in order to manage the disease. In addition to educational programs for patients and medical professionals, SAA provides information through the SAA website[1], a bimonthly news magazine (*Spondylitis Plus*), and multiple educational brochures, such as "Childhood Onset SpA," "SpA: A Family of Related Diseases," "The Role of Exercise in SpA," and "Iritis (Eye Inflammation) in SpA."

Highlights of Basic Science Presentations

Robert Colbert, MD, PhD, (Cincinnati Children's Hospital Medical Center, Ohio) presented a brief history of the human leukocyte antigen B27 (HLA-B27) and reviewed various hypotheses that attempt to explain its role in the pathogenesis of SpA. He focused on emerging data from recent studies showing that HLA-B27 has aberrant features that may underlie its role in disease[2]. Notably, this protein has a propensity to misfold during its formation inside the cell, leading to activation of endoplasmic reticulum stress pathways that trigger the "unfolded protein response"[3], with consequent innate immune activation. HLA-B27 also appears in aberrant forms on the cell surface, which may trigger the immune system through immunological recognition[4]. Dr. Colbert stressed that it is still unknown if recognition of HLA-B27 by effector cells is involved in the pathogenesis of disease or if the key effects of HLA-B27 are intracellular. It is also conceivable that more than one characteristic of HLA-B27 may be important in the pathogenesis of SpA.

John Reveille, MD, (University of Texas, Houston) reviewed recent research on the role of genetics in predicting suscepti-

bility to AS. He reminded the group that < 5% of HLA-B27-positive people in the general population develop SpA. On the other hand, 20% of HLA-B27-positive relatives of patients with AS develop SpA. Studies of family genetics suggest that HLA-B27 forms only about 37% of the overall risk for SpA. The entire effect of the major histocompatibility complex (MHC) is about 50%. Dr. Reveille summarized the results of metaanalyses of 3 recent genome-wide scans[5-7]. Although there was variability among the metaanalyses, the studies showed predominant associations with regions on chromosomes 3q, 5q, 6p, 10q, and 16q. Dr. Reveille discussed plans for a more comprehensive genome-wide association study. Additionally, he presented recent studies of candidate gene markers, including those in the interleukin 1 region and neural cell adhesion molecule 1 (NCAM-1).

Robert Inman, MD, (Toronto Western Hospital, University of Toronto, Toronto, Ontario) spoke about the challenges of early identification of the pathogenesis of AS. He presented results from recent studies in his laboratory on the biology of reactive arthritis, as analogs that might provide clues to the pathogenesis of AS. These included mechanisms by which *Chlamydia* persists as an intracellular pathogen by actively thwarting apoptosis[8], the importance of variation in neutrophil Rac protein expression in the severity of *Chlamydia*-induced arthritis in animals[9], and osteoclast activation by synovial fibroblasts infected with *Salmonella*[10]. Dr. Inman also reviewed the results of studies on osteoclast precursors[11] and recent studies on the role of the progressive ankylosis (ank) gene in familial spondylitis[12], the interleukin 1 (IL-1) gene[13], and the correlation of serum bone morphogenetic proteins with disease activity in AS[14].

Highlights of Clinical Presentations

Harry Genant, MD, (University of California, San Francisco, CA) discussed the role of imaging for diagnosis of sacroiliitis and its use in tracking anatomical changes in the spine, peripheral joints, and entheses in patients with SpA. The sacroiliac (SI) joint is one of the most difficult joints in the body to image, because of its complex anatomy and undulating articular surfaces. Conventional radiographs remain the method of choice in clinical studies of established AS and for detecting chronic changes (i.e., syndesmophytes), but they are unable to detect early inflammatory changes of sacroiliitis, which is important for timely diagnosis. Bone scintigraphy is sensitive to inflammatory changes in the SI joints and may reveal disease activity, but it lacks specificity. Computed tomography (CT) effectively shows cortical erosions, subchondral sclerosis, and other bony abnormalities, but cannot detect active inflammatory changes within subchondral bone. Magnetic resonance imaging (MRI) is the only imaging technique that can detect actively inflamed lesions in the SI joints, as well as in the rest of the skeleton. Thus, MRI is the most helpful technique for detecting acute sacroiliitis and spinal inflammation in early disease stages. Dr. Genant suggested that MRI, especially contrast-enhanced MRI, may soon become the gold standard for assessing and documenting the efficacy of antiinflammatory drugs for SI and spinal inflammation[15].

Dafna Gladman, MD, FRCPC, (University of Toronto, Toronto, Ontario) reminded the group that psoriatic arthritis (PsA) is classified among the seronegative SpA because of its clinical features and its association with HLA-B27. Since 2000, comparisons of demographic and clinical features of patients with PsA, nonpsoriatic SpA [AS and undifferentiated SpA (uSpA)], and rheumatoid arthritis (RA) have led to the conclusion that the synovial histopathology of PsA resembles SpA more than RA. Dr. Gladman emphasized a recent demonstration of the role of dactylitis as a marker of disease severity in PsA. She also summarized the results of clinical trials of new biologics, specifically anti-TNF agents and T cell-directed agents, and their comparative effects on joint disease (clinical and radiographic), psoriasis, other PsA manifestations (dactylitis, tendonitis, spondylitis), and quality of life. Dr. Gladman concluded with a discussion of the Classification of Psoriatic Arthritis (CASPAR) study, a recently completed prospective, observational study designed to compare the performance of existing PsA classification criteria with new criteria derived from observed data. The CASPAR study validated a new standard for definition of PsA, e.g, inflammatory musculoskeletal disease (joint, spine, or entheseal), with ≥ 3 of the following criteria: current psoriasis (or personal or family history of psoriasis), psoriatic nail dystrophy, rheumatoid factor negativity, dactylitis (current or ever), and radiological evidence of juxtaarticular new bone formation[16]. Dr. Gladman also announced formation of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), which will assist in developing assessment tools, promoting basic research, and fostering interdisciplinary and general communications about PsA.

Robert Inman, MD, (Toronto Western Hospital, University of Toronto) reviewed recent findings[17] from the AS Life Impact Survey, a survey of 7500 subjects registered with the SAA. The objective of the study was to compare functional outcome in juvenile onset AS (JoAS; disease onset < 16 years of age) to adult onset AS (AoAS), and to identify variables associated with poor functional outcome in JoAS. Dr. Inman reported that JoAS more frequently involves peripheral disease at onset, compared with AoAS. According to the study, patients with JoAS had worse functional outcomes and more work disability. Also, females with AS have worse outcomes than males. It appears to be important to diagnose and treat patients with AS early in the course of disease. Dr. Inman also discussed the Stone-Bruckel self-assessment spinal deformity tool for AS, developed at the SAA[18]. This cartoon instrument demonstrated good construct validity, and could be useful in

studies assessing functional impairment and spinal deformity in patients with AS.

Michael Ward, MD, [National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH/NIAMS)] discussed the heterogeneity of the causes of functional limitations in AS and said that risk factors may be overlooked, or the degree of risk mis-specified, in studies of unselected groups of patients. He presented initial results of the Prospective Study of Outcomes in AS (PSOAS) study, in which the primary goal was to identify genetic influences on disease severity in patients with long-standing AS (≥ 20 years)[19]. In this study, functional limitations appeared to be more severe among patients with a history of physically demanding jobs, among smokers, and in patients with more comorbidities, and less severe among patients with higher levels of education and a family history of AS. Dr. Ward also discussed the Occupational Information Network (ONET), a US Department of Labor job classification database, which was used to rate specific activities of the occupations engaged by the PSOAS study subjects. Bending and twisting were identified as specific occupational activities most closely associated with greater functional limitations.

John Davis Jr, MD, MPH, (University of California, San Francisco) updated the group on several reports on recommendations for the treatment of patients with AS, including the use of anti-TNF agents. Recommendations included those developed by ASAS and the European League Against Rheumatism (EULAR) using a systematic literature review, expert opinion, and Delphi exercises, which were reported in June 2005[20,21]. Dr. Davis then provided a comprehensive overview of the 2003/2005 ASAS recommendations for treatment of AS, followed by a summary of US-specific (SPARTAN) modifications[1,22]. The SPARTAN modifications include the use of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; ≥ 4 cm on a scale of 0–10) and a physician global assessment (> 2 on a scale of 0–4) for the initiation of anti-TNF therapy and as criteria for and timing of a clinically meaningful improvement[1,23]. Failure or intolerance of ≥ 2 nonsteroidal antiinflammatory drugs (NSAID) should be required for axial manifestations, peripheral arthritis, and enthesitis. Failure with disease modifying antirheumatic drugs such as sulfasalazine or methotrexate should be required only for peripheral arthritis and not for axial manifestations or enthesis. No injections of enthesitis should be required.

Breakout Session: Epidemiology

Moderators: John D. Reveille, MD, and Michael H. Weisman, MD

It is extremely important to identify the true incidence and prevalence of AS and SpA in the North American population, not only for patient-centered issues (early diagnosis and definitive management), but also for public policy issues. Investigators were informed of plans and progress on 2 research projects. John Reveille, MD, (University of Texas Houston Medical School) described a module that has been proposed for the 2007 National Health and Nutrition Examination Survey (NHANES): a population survey to estimate the prevalence of axial SpA in the US by measuring inflammatory back pain, limitation of spinal mobility, and HLA-B27 typing. It was noted that spinal imaging, either by standard radiographs or by MRI, will not be possible in this module, and the limitations relative to the diagnosis of axial spondyloarthritis were discussed by the group. A pre-NHANES validation study was suggested, using cohorts of patients with pelvic radiographs already available, such as the Framingham Study or the Carolina Osteoarthritis project. Michael Weisman, MD, (Cedars-Sinai Medical Center, Los Angeles, CA) described a 4-phase plan to develop and validate a screening questionnaire for inflammatory back pain that will identify patients at very high risk for AS. The team is designing a study protocol and finalizing an initial questionnaire. Their plan is to perform a case-control study of 100 patients, validate the diagnostic tool, and develop an online version of the tool. One limitation of this tool will be that inflammatory back pain is the entry point to identify all patients; if AS patients present with only extraspinal disease, they will not be identified. The group discussed the limitations of not having a "gold standard" such as radiographic evidence, and it was suggested that a substudy using imaging might be entertained in order to prevalidate the questionnaire.

Breakout Session: Pediatrics

Moderators: Robert Colbert, MD, PhD, and Christy Sandborg, MD

The group discussed the classification, early detection, and treatment measures of SpA in the pediatric population. The classification of undifferentiated SpA in children differs from adults, in part reflecting infrequent spinal involvement at disease onset. The International League of Associations for Rheumatology (ILAR) has proposed enthesitis-related arthritis (ERA) as a category for uSpA in children[24], to distinguish jSpA from other forms of juvenile idiopathic arthritis. This classification system excludes individuals with psoriasis or a family history of this disease. The group discussed the need to validate the ERA classification system and determine whether it predicts axial disease, or to use the adult classification system for uSpA whenever possible and reserve ERA for patients who do not meet these criteria.

The recent focus on early recognition of spinal disease is a particularly relevant issue in the pediatric population. It will be important to identify genetic and biologic markers present in patients with non-axial, undifferentiated disease who are predisposed to this phenotype. These markers must be assessed in longterm studies of pediatric and adult patients.

The efficacy of TNF inhibitors in AS has been documented in several studies of adult patients and more recently in

jSpA[25]. It will be important to define indications for use of TNF inhibitors in pediatric patients who do not have spinal disease. Appropriate measures of disease activity and outcome in children must be developed, since measures used in adult studies of AS may not be sufficiently sensitive for juvenile-onset disease in the absence of spinal involvement. The group plans to meet again to further discuss research in jSpA.

Breakout Session: Treatment Controversies in Ankylosing Spondylitis

Moderators: John Davis Jr, MD, MPH, and Atul Deodhar, MD

Multiple studies have shown that anti-TNF agents are the only treatments that have any effect on axial manifestations of AS and may actually be structure-modifying. The question remains, however, which patients should be treated with anti-TNF agents, and especially if they should be used on patients without radiographic evidence of bilateral sacroiliitis that meets modified New York criteria. To date, few open-label or case-series have been reported using anti-TNF agents in patients that do not meet modified New York criteria. The general belief is that these patients may benefit from therapy, so there is a need to expand upon the current state of the art recommendations[1,20-23,26]. Many rheumatologists are not using instruments designed to detect clinical response [e.g., the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and physician global assessment] when initiating and monitoring patients on anti-TNF therapy. SPARTAN acknowledges that guidelines should be followed in the initiation and continuation of anti-TNF therapy, and believes the BASDAI and physician global should be used in clinical practice. It is clear that future guidelines need to be less restrictive and more relevant and applicable to the clinical practice. Therefore, it was recommended that a patient's willingness to take anti-TNF agents (and the associated risks) should be included as initiation criteria. Future steps and further research are needed in the following areas: (1) What is the optimal length of time to be undergoing anti-TNF treatment (lifelong?); (2) What is the role of MRI, both in making the diagnosis of axial SpA and in detecting inflammation, and can this be used to monitor response; (3) Are anti-TNF agents truly disease-modifying; and (4) What are the additional risk factors for poor outcome in SpA (e.g., rapid radiographic progression, elevated C-reactive protein, MRI inflammation, etc.). SPARTAN will modify these guidelines on a yearly basis with emphasis on issues related to the US.

Highlights of Fellows' Sessions

Eleven rheumatology fellows from training programs across the continent participated in an educational session with conference faculty. Topics included "Overview and Epidemiology of AS" (with John Cush, MD, and Muhammad Khan, MD); "Extra-axial Disease" (Jim Rosenbaum, MD); "Radiology" (Tom Learch, MD); "Outcome Measures for Clinical Practice and Research" (John Davis Jr, MD, MPH); "Treatment" (Atul Deodhar, MD); and a "Patient Centered Exercise" (Drs. Daniel Clegg, John Cush, John Davis Jr, Atul Deodhar, Muhammad Khan, John Reveille, Jim Rosenbaum, Michael Weisman, and David Yu). In addition, fellows presented their current research in a session of the general meeting.

Future Plans of SPARTAN

In the coming year, SPARTAN plans to develop a Web-based learning module for trainees; continue the support of ongoing and planned clinical research projects; support a conference dedicated to pediatric SpA; and publish in a peer-reviewed journal an editorial focused on the use of TNF antagonists in the treatment of AS. In addition, many members of SPARTAN will be involved in "Spondyloarthritis 2006: The Unmet Needs," an SAA and NIAMS conference March 30-31, 2006, in Bethesda, Maryland.

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