Meeting Report

2006 Annual Research and Education Meeting of the Spondyloarthritis Research and Therapy Network (SPARTAN)

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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 interested in promoting research, education, and treatment of spondyloarthritis (SpA). In past years, it has produced and disseminated United States-specific modifications of the ASsessments in Ankylosing Spondylitis (ASAS) guidelines for the use of anti-tumor necrosis factor (TNF) therapy in AS[1]. SPARTAN held its fourth annual research meeting in July 2006 in San Francisco, California. Highlights of the meeting included an update on the past, present, and future of epidemiologic research of SpA. Participants also heard updates on the pathogenesis of SpA and a report on the use of magnetic resonance imaging (MRI) in SpA. A discussion was held on disease modification properties and potential side effects of anti-TNF agents in patients with SpA. An educational pre-meeting conference was specifically designed for rheumatology fellows.

Epidemiology of spondyloarthritis

The past: Epidemiology of SpA — US and worldwide. Muhammad Asim Khan, MD, MACP, FRCP (Case Western Reserve University, Cleveland, Ohio). Dr. Khan discussed the prevalence of AS and related SpA. The reported prevalence of AS ranges between 0.1% and 0.8%, and recent studies suggest that it is closer to 0.5% in European populations, especially in northern Europe[2-5]. A very recent population-based epidemiological study of AS and SpA in Izmir, Turkey, reported a 0.49% prevalence of AS[6]. The prevalence of SpA as a whole (including AS) is about 1%, based on European Spondylarthropathy Study Group (ESSG) criteria[7]. In the recent Turkish study, the prevalence of SpA was reported to be 1.05%, and it was observed to be 0.47% in Brittany, France; in both studies, SpA was almost equally prevalent in males and females[6,8].

In a German study of HLA-B27+ blood donors in Berlin (with 9% HLA-B27 prevalence), the prevalence of SpA (including AS) in the general population was calculated to be 1.73%[9,10]. The prevalence of AS was calculated to be 0.55% in the general population and 6.4% in the HLA-B27+ population[9,10]. In an older epidemiological study of a middle-aged population in northern Norway, where the HLA-B27+ population is 16%, the prevalence of AS was 1.1%–1.4% in the general population and 6.7% in the HLA-B27+ population[4]. Generally speaking, although there are some exceptions, the disease prevalence roughly correlates with the prevalence of HLA-B27[3,11].

Dr. Khan stated that there are no current population-based epidemiological studies of AS and SpA in the US, but based on data from the National Health and Nutrition Examination Surveys (NHANES), the estimated prevalence of all forms of SpA (including AS) may be much higher than previously reported[12]. He emphasized that because of the availability of more effective treatments, early diagnosis of these diseases is critical[13]. He then led a discussion of which measures should be used for screening for inflammatory spine diseases, and emphasized the need to develop diagnostic criteria for AS and related SpA[13].

The present: The NHANES project. John D. Reveille, MD (University of Texas, Houston). Dr. Reveille listed the challenges in determining the epidemiology of SpA, including disease heterogeneity, varied classification criteria[14,15], the transient nature of arthritis and enthesitis in patients with peripheral involvement, the lack of feasibility of MRI and pelvic radiographs, and the lack of reliable biomarkers. He then described the design and results of the NHANES I project, a representative study conducted among 6913 par-

ticipants 25–74 years old at 100 locations in the US between 1971 and 1975. Pelvic radiographs were obtained in all but 2010 participants (predominantly women < 50 yrs old), and each radiograph was read independently by 2 expert rheumatologists and graded on a scale based on the *Atlas for Standard Radiographs*[16]. Results are available online at www.cdc.gov/nchs/data/nhanes.htm. Dr. Reveille noted several problems revealed by the NHANES I project: 54% of participants who had moderate to severe radiographic sacroiliitis reported never being treated for joint problems, and only 7.6% were currently experiencing significant lower back pain. Sacroiliitis was probably underestimated; post-study, it was determined that the knee and hip readings for osteoarthritis were under-read and the same rheumatologists read the pelvic radiographs. Moreover, the overall grade for disease was an average between bilateral sites, which may have diluted the scores if only unilateral disease was present, and questions regarding inflammatory back pain (IBP) and measurements of spinal mobility were not asked.

The proposed NHANES 2009 study of axial SpA, currently under development, will address some of these concerns by assessing characteristics of IBP, limitations of spinal mobility (such as modified Schöber test, occiput-to-wall distance, and chest wall expansion), and HLA-B27 typing. However, further work is necessary before it can be considered for inclusion in NHANES, including validation of IBP questions (which are being modified from the instrument developed in Europe)[15] and collecting population-based data on spinal measurements. Both will be necessary because obtaining confirmatory pelvic radiographs in a large population study is no longer feasible. Dr. Reveille led a discussion of the feasibility of the proposed NHANES SpA component, suggesting that it could be amended to add additional questions (i.e., uveitis), modify the metrology, and include C-reactive protein. Above all, it will need to be validated in a cohort of patients with established AS [e.g., the Prospective Study of Outcomes in AS (PSOAS)] as well as in patients with IBP and mechanical back pain.

The role of US National Health Surveys in epidemiologic studies of SpA. Rosemarie Hirsch, MD, MPH (Centers for Disease Control and Prevention, Atlanta, Georgia). Dr. Hirsch listed the challenges of studying SpA in any epidemiologic study, including its low prevalence, the need for validated questionnaire instruments and classification criteria protocols, and the cost of radiographic readings. Dr. Hirsch then described the goals of NHANES surveys (www.cdc.gov/nchs/nhanes.htm) as they relate to SpA, the primary one being to estimate the prevalence and risk factors for disease in the US population and in designated subgroups. She described the sampling and design of NHANES, which began in 1960, and how data are collected using a unique combination of in-home interviews and examinations conducted in mobile examination centers. Some, but not all, necessary data relevant to SpA have been successfully collected in prior NHANES, and estimates for other low prevalence rheumatic conditions have been produced from NHANES data. However, at least 4–6 years of data collection would be necessary to produce accurate estimates for SpA because it is such a low prevalence condition. Dr. Hirsch concluded by describing the proposal process for including an SpA component in NHANES. (Note: The findings and conclusions in this section are those of the author and do not necessarily represent the views of the CDC.)

The future: Methods and current research for prevalence. Sherine Gabriel, MD, MSc (Mayo Clinic College of Medicine, Rochester, Minnesota). Dr. Gabriel spoke of the need to stimulate future epidemiology research in AS, especially its prevalence, by placing AS in the broader context of musculoskeletal (MSK) disorders and considering the relevance of AS to MSK. She reminded the group that MSK and rheumatic conditions are a major cause of morbidity, with corresponding economic burden and influence on quality of life. Dr. Gabriel summarized the results of a World Health Organization (WHO) 2003 report[17], which outlined the global burden of MSK disorders at the beginning of the millennium, estimated their future magnitude and economic impact, and provided a strategy to achieve more effective prevention and/or treatment. She suggested that this report could guide future epidemiology research in AS. Specifically, the report identifies the lack of standardization and validation in diagnosing and classifying spinal disorders as a major impediment for improved prevention and/or treatment. In addition, the recent emergence of IBP as a distinct clinical entity raises the question of whether inflammation or IBP play a role in low back pain (LBP), a condition that affects some 80%–85% of the worldwide population. Thus, valid diagnostic and classification criteria are not only essential for the study of IBP but may also lead to new insights into the pathogenesis of AS, SpA, and LBP.

Dr. Gabriel underscored the importance of research to improve our understanding of the epidemiology and outcomes of AS and SpA by highlighting the global importance and lifelong effects of these disorders. She also shared data demonstrating the increased risk of mortality, specifically of cardiovascular mortality, among persons with AS. Finally, Dr. Gabriel highlighted the recent introduction of new biologic agents for the treatment of AS and SpA, indicating that a thorough assessment of their risks and benefits requires a more complete understanding of the incidence, prevalence, and outcomes of these disorders. For all of these reasons, Dr. Gabriel argued for a coordinated approach to define the incidence, prevalence, and outcomes of IBP, AS, and SpA in the broader context of LBP and other spinal disorders. While the WHO suggests it is urgent to define the incidence and prevalence of MSK disorders, Dr. Gabriel concluded that it is equally urgent to define the epidemiology and outcomes of AS, IBP, and SpA.

Pathogenesis of spondyloarthritis: an update

J.S. Hill Gaston, MA, PhD, BM, BCh, FRCP, FMedSci (University of Cambridge, England). Dr. Gaston reviewed the much-researched role of HLA-B27 in the pathogenesis of SpA. He noted that the role of B27 has been explored in 2 broad ways: research into HLA-B27's allele-specific and physiologic properties, i.e., its ability to present peptides to the immune system (CD8+ T cells), and research into allele-specific and idiosyncratic properties, e.g., the ability of B27 to present the same peptide in 2 different configurations that are distinguishable by T cells. Dr. Gaston then summarized recent research on additional idiosyncratic properties, including abnormalities in the assembly of B27 and its acquisition of antigenic peptides independent of tapasin; a tendency for the heavy chain to misfold and provoke a cellular unfolded protein response; an effect on antigen-presenting cell function including the handling of intracellular bacteria; and the ability to be expressed in unusual ways (free heavy chain, homodimers) at the cell surface, resulting in novel interactions with T cells and other immune effectors.

In transfection experiments, B27 subtypes associated with SpA (B*2704, B*2705) were compared with 2 not associated with disease (B*2706, B*2709). Only B*2704 was found to be partially tapasin-dependent[18]. When incorporation of B27 heavy chains into the peptide loading complex [tapasin and transporter associated with antigen-processing (TAP)] was examined, B*2706 was found to be poorly associated. Thus, a subtype not associated with disease was paradoxically shown to be more liable to be expressed as free heavy chains on the cell surface.

In transcriptome analysis, HLA-B27 did not have a major effect on the response to lipopolysaccharide (LPS) in a transfected macrophage-like cell, nor did LPS treatment provoke an unfolded protein response[19]. Similarly, no effect of B27 expression was observed on uptake and growth of *Chlamydia*, suggesting that HLA-B27 does not grossly interfere with antigen-presenting cell function[20]. However, B27 does interact in unusual ways with lymphocytes, since it can be recognized by CD4+ T cells. Evidence from one clone suggested an interaction involving recognition of either peptide-less B27 or homodimers[21]. Additional CD4+ T cell clones recognized B27-derived peptides presented by both Class I and Class II MHC alleles. Whether such T cell recognition is critical to SpA pathogenesis has not been determined.

Finally, an unusual property of dendritic cells from patients with SpA has been noted: coculture of CD8+ T cells with LPS-activated dendritic cells from patients with SpA results in generation of interleukin 4-producing cells that are autoreactive and have phenotypic and functional properties similar to those of CD4+CD25+ regulatory cells[22]. In summary, recent evidence suggests that SpA is an outcome of genes (B27 and others) acting within dendritic cells to influence the generation of a "spondylito-genic" T cell response.

Use of MRI in SpA and its role in the future

Mikkel Østergaard, MD, PhD, DMSc (Copenhagen University Hospitals at Herlev and Hvidovre, Denmark). Dr. Østergaard reminded the group that while symptoms of AS normally begin in young adulthood, 7–10 years may pass before it is diagnosed, during which time significant permanent damage often has occurred. He stressed a need for better diagnostic criteria than the modified New York[14] or ESSG[7] classification systems, and for better outcome measures than the commonly used ASAS core set[23]. He suggested that the ideal method would be reliable and useful in diagnosis, monitoring, and perhaps even prognostication. He noted that MRI is very promising, because it allows a more complete assessment of the disease due to its ability to visualize all affected structures.

Dr. Østergaard then reviewed recent knowledge on optimal MR image acquisition, noting that intravenous contrast medium injection may not be necessary for reliable assessment of disease activity[24,25]. He compared MRI with computed tomography (CT), saying it is diagnostically comparable with regard to bone erosions, but that MRI can detect sacroiliitis before CT because it reveals earlier signs of activity in the bone marrow and joint space. Further, MRI involves no ionizing radiation. Dr. Østergaard also said that MRI has been shown to have greater sensitivity and specificity than radiography or scintigraphy in diagnosing arthritides, including axial SpA, but that the optimal diagnostic approach needs to be determined[26-28].

Dr. Østergaard next discussed the scoring systems for assessment of inflammation in the sacroiliac (SI) joints[29] and spine[30], citing results from a recent study comparing the AS-spiMRI-a, Berlin, and SPARCC (Spondyloarthritis Research Consortium of Canada) methods. He also reviewed results from other recent studies in which MRI was used to assess therapeutic efficacy in AS patients treated with infliximab, etanercept, or adalimumab[31-34].

Dr. Østergaard concluded that the current data clearly establish MRI as a very sensitive method for detection of sacroiliitis and spondylitis. He said we now have MRI methods that are reliable and sensitive to change and that allow discrimination between active and inactive therapies. Finally, he stressed the need for further research and recommended that studies should focus on MRI's prognostic value regarding radiographic changes and functional outcome and its exact clinical value in the diagnosis and monitoring of SpA.

Treatment aspects of anti-TNF disease modification: properties and potential side effects

Disease modification properties of anti-TNF agents. John C. Davis, MD, MPH (University of California, San Francisco). Dr. Davis summarized disease modification properties of anti-TNF therapy in AS, including improvements in the ASAS 20 criteria, Bath AS Disease Activity Index (BASDAI), metrology, function, inflammatory MRI changes,

bone mineral density, markers of bone and cartilage metabolism, acute phase reactants, and limited radiographic data.

Analyzing disease modification in AS raises several issues: Should disease modification include structural change? Is a major clinical response evidence of disease modification? Another issue has been our reliance on a rheumatoid arthritis (RA) model. In AS, change in the spine is not easily viewed, and the optimal time to detect change is unknown. Additionally, we do not know the correlation of short-term MRI changes with radiographic outcomes. Finally, no true placebo group exists, and we cannot give placebo to patients with active disease for long periods of time.

Of the radiographic scoring systems, the modified Stoke AS Spinal Score (mSASSS) was recommended by Outcome Measures in Rheumatology Clinical Trials (OMERACT) 2004. The mSASSS has been validated in patients with long disease duration but has not been used widely in clinical trials. A European group, which used the mSASSS in a longitudinal cohort of patients with AS, reported that only baseline damage was predictive of radiographic progression, and that at least 2 years was needed to detect a 1.5 change in mSASSS[35].

In a retrospective analysis, patients with AS treated with continuous nonsteroidal antiinflammatory drugs (NSAID) reportedly had less radiographic progression over a 2-year period compared with those treated as needed[36,37]. However, the changes were small: 0.4 versus 1.5, respectively.

Previous data from uncontrolled trials of etanercept[38] and infliximab[39] have shown that radiographic progression was diminished compared to published cohorts, but was not completely halted[39,40]. These data should be interpreted with caution and may be biased, as readers were aware of the origin of the radiographs and different readers were used.

Recently, radiographic data from patients with AS treated with etanercept for 2 years were compared with the Observational Arthritis Study in Seniors (OASIS) cohort using the mSASSS[38]. Images were scored by 2 independent readers, who were blinded to the origin and sequence of the radiographs. The mean change in the etanercept group was 0.91 versus 0.95 in OASIS. In a subgroup of OASIS patients with comparable BASDAI scores, the mean change was 1.27 (p = nonsignificant). These data suggest that although inflammatory processes are suppressed with anti-TNF therapy, progression of structural damage may continue. Further, unlike the RA model, where suppression of inflammation decreases structural change, suppression of inflammation in AS may not lead to a reduction of new bone formation. Radiographic results are pending in studies of other anti-TNF agents.

Although radiographic data in patients with AS are meager, major clinical responses have been demonstrated with anti-TNF agents. Current recommendations for the use of anti-TNF agents are still appropriate, and patients should be treated accordingly[23,41].

Is there evidence of increased malignancy among AS patients? Daniel O. Clegg, MD (University of Utah, Salt Lake City, Utah). Dr. Clegg summarized the available malignancy data in HLA-B27-positive individuals and in patients with AS and psoriasis, and concluded that while data are meager, increases in malignancies are slight and are predominantly hematologic. In a Chinese study of 1137 HLA-typed patients, 59 patients (5.2%) were HLA-B27-positive; 4 of these patients had AS and all had lymphoid malignancies (3 acute lymphoblastic leukemia, one Hodgkin's disease)[42]. In a Swedish registry study of 6621 patients with AS admitted to hospital from 1965 to 1995, no overall increase in cancer risk was observed. A decreased risk of rectal cancer was observed, however, possibly due to local applications of NSAID; and unspecified kidney cancer was somewhat increased, for which one suggested reason was increased exposure to pelvic radiation[43]. In another Swedish registry study 1964–2000 of 50,615 lymphoma patients and 92,928 controls, patients with AS showed no increased risk of lymphoma (odds ratio = 1.3)[44]. Lymphoma risk also was assessed in a preliminary report from the United Kingdom General Practice Research Database (GPRD) of 3262 patients with AS who were compared with 26,948 patients with RA and followed 1994–2001; incidence rates were 50 and 73 for patients with AS and RA, respectively, compared with 17 for the general population[45]. In another United Kingdom GPRD, 2218 patients with psoriasis and 105,203 controls ≥ 65 years old were followed 1988–96; patients with psoriasis had a 2.95 relative risk of developing lymphoma, compared with controls[46].

Dr. Clegg also discussed the risk related to colorectal cancer (CRC) in patients with IBD. He summarized results from 2 studies that both suggested that CRC is not as common in IBD as previously considered. In a prospective followup of 600 patients who underwent 2627 colonoscopies over a 30-year period, the cumulative incidence of CRC was 2.5%, 7.5%, and 10.8%, at 20, 30, and 40 years, respectively, and the authors concluded that colonoscopic surveillance was effective[47]. In the Rochester Epidemiology Project, 692 patients with IBD were followed between 1940 and 2001; CRC was observed in 6 patients with ulcerative colitis (4 with extensive pancolitis) and in 6 patients with Crohn's disease (CD), and 3 patients with CD developed small bowel cancer[48].

Side effects of anti-TNF agents including malignancy in AS. Anthony M. Turkiewicz, MD (University of Alabama at Birmingham). Dr. Turkiewicz used data from published clinical trials and national registries, the Food and Drug Administration Freedom of Information Act, and information from pharmaceutical companies to compile his review of the safety of anti-TNF agents in patients with AS. He concluded that the overall safety was similar to that seen in patients with RA and psoriatic arthritis (PsA) based on currently available data, but that the safety dataset for anti-TNF

agents in AS is still lean at this time, particularly with regard to longterm data on rarer serious adverse events such as malignancy and demyelinating disorders.

In the initial published accounts of infliximab in AS, notable reported adverse events were 4 cases of lupus-like syndrome and one of tuberculosis (TB)[49,50]. Dr. Turkiewicz noted that these early trials enrolled patients prior to TB screening guidelines currently recommended for anti-TNF use. In a systematic review of 107 patients (61 AS, 29 PsA, 14 undifferentiated SpA) treated with infliximab, 2 cases of TB reactivation (neither patient was screened for TB), 3 of retropharyngeal abscesses, and 3 of palmoplantar pustolosis were reported, but no malignancies were attributed to therapy and no case of heart failure or lupus-like syndrome was reported[51]. In the ASSERT study of 275 patients with AS (200 infliximab, 75 placebo), 7 infliximab patients had serious adverse events, compared with 2 patients in the placebo group; however, no deaths, malignancies, or TB cases were reported[52].

Published accounts of clinical trial experience of etanercept in patients with AS are also available[53-56]. The incidence of adverse events (serious and non-serious) was similar between the etanercept and placebo groups, and no increases in rates of events between the controlled trials and open-label extensions were observed.

Similar findings have been observed with adalimumab. In an open-label pilot study of 15 patients with AS treated with adalimumab for 52 weeks, no serious adverse events related to study drug occurred and no serious infections were observed; of note, in 3 patients whose skin tested positive for TB and who had initiated a 9-month course of isoniazid 4 weeks before adalimumab administration, no reactivation of TB was observed[34]. In the ATLAS study, a randomized (2:1), double-blind, placebo controlled, 24-week trial of 315 patients with AS, the safety profile of adalimumab was consistent with that observed in patients with RA and PsA[57].

Dr. Turkiewicz then presented biologic safety data from 2 large registries, the British Society for Rheumatology Biologics Register (BSRBR)[58] and the Spanish Society of Rheumatology Database on Biologic Products Drug Registry (BIOBADASER)[59,60]. Although these data suggest a somewhat safer adverse event profile with anti-TNF agents in patients with AS/SpA compared with that observed in patients with RA, Dr. Turkiewicz suggested that longterm safety data are needed to more accurately assess the significance of these observational data.

Highlights of fellows meeting

Twenty rheumatology fellows from training programs in the US and Canada participated in a half-day review course on SpA the day before the general meeting. Topics included "Pathogenesis and Genetics of SpA" (David Yu, MD), "Early Diagnosis of SpA" (Michael Weisman, MD), "Extra-articular features of SpA" (Daniel Clegg, MD), "Imaging in SpA: Role of MRI" (Tom Learch, MD), "Treatments and Best Practice Guidelines" (Atul Deodhar, MD), and a patient-centered exercise that included patient perspectives, examination, metrology, etc. (Drs. John Davis Jr, Atul Deodhar, Daniel Clegg, Michael Weisman, and David Yu).

Future plans of SPARTAN

SPARTAN will continue to support clinical research projects and a Web-based learning module for trainees. Our fifth Annual Research and Education meeting will be held September 14-15, 2007, in Cleveland, Ohio (see www.spartangroup.org).

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