Entheses and Bones in Spondyloarthritis: 2008 Annual Research and Education Meeting of the Spondyloarthritis Research and Therapy Network (SPARTAN)

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ABSTRACT. The Spondyloarthritis Research and Therapy Network (SPARTAN) was founded in 2003 by a group of North American clinicians and researchers who meet yearly to promote research, education, and treatment of ankylosing spondylitis (AS) and related forms of spondyloarthritis (SpA). At the 6th annual SPARTAN research meeting in July 2008 in Cleveland, Ohio, the overall theme was entheses and bones in SpA. Presentations focused on the anatomy and physiology of the synovial-entheseal complex; bone formation and destruction, and the effect of inflammation on bone; and controlling the Th17 axis. There was also a discussion of HLA-B27, IL23R, and ARTS1, and breakout sessions on epidemiology and registries. (J Rheumatol 2009;36:1527–31; doi:10.3899/jrheum.090122)

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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)1-3. At the 6th annual SPARTAN research meeting in July 2008 in Cleveland, Ohio, the overall theme was entheses and bones in SpA. Presentations focused on the anatomy and physiology of the synovial-entheseal complex; bone formation and destruction, and the effect of inflammation on bone; and controlling the

Th17 axis. There was also a discussion of HLA-B27, IL23R, and ARTS1, and breakout sessions on epidemiology and registries. An educational pre-meeting conference was specifically designed to further discuss the genetics, pathogenesis, diagnosis, and treatment of ankylosing spondylitis (AS) with 25 rheumatology fellows.

Anatomy and Physiology of the Synovial-Entheseal Complex (SEC) in Spondyloarthritis. Dennis McGonagle, PhD, FRCPI (University of Leeds, UK) stated that chronic synovitis in SpA results in bone and cartilage erosion analogous to rheumatoid arthritis (RA)4. However, the fundamental difference between SpA and RA is that SpA is enthesis-based pathology. Dr. McGonagle discussed how the enthesis is more than merely a focal attachment and described the enthesis organ components, including the attachment site, adjacent bony tissue, bony tuberosities near insertions, and adjacent fibrocartilage and synovium. He said some structures (including tendons at points where they wrap around bone and fibrocartilagenous synovial joints) behave as “functional enthesis” and share identical anatomy, histology, mechanics, and pathology5. Inflammation at the enthesis or functional enthesis is associated with osteitis, with severity of osteitis in the axial and peripheral skeleton also related to the HLA-B27 gene6. Further, microdamage and repair responses are common features of the aged enthesis, suggesting that HLA-B27 may affect sites of microdamage7.

Dr. McGonagle demonstrated the relationship between enthesitis and synovitis in SpA with a diagram from a recent
study of the SEC in the Achilles tendon\(^8\). He used several images of synovial changes, enthesal inflammation, and synovial damage of the enthesis in SpA to summarize the SEC changes, showing that microdamage is common along the enthesis and is associated with inflammation and adjacent synovitis, and all regions of inflammation are interlinked\(^9,10\). He also discussed the emerging role of the enthesis and SEC in erosive osteoarthritis and RA erosion formation\(^11\). Dr. McGonagle concluded that the SEC is important for understanding joint inflammation in RA is, of more general importance in RA, and exists to minimize damage at sites of high mechanical stress.

**Bone Formation and Destruction: What Controls the Balance?** Ellen M. Gravallese, MD (University of Massachusetts Medical Center, Worcester, MA) demonstrated the mechanisms of focal bone erosion that often result in debilitating joint destruction, using results from RA studies in her laboratory. She demonstrated that receptor activator of nuclear factor-\(\kappa\)B ligand (RANKL), a required factor for osteoclast differentiation, is expressed at sites of articular bone erosion in RA\(^12\). Expression of its receptor, RANK, correlates with progression of inflammation in collagen-induced arthritis (CIA)\(^13\). In addition, in RANKL or c-fos-deficient mice that cannot make osteoclasts, arthritis and cartilage destruction occur, but articular bone is protected from erosion, demonstrating that osteoclasts mediate bone resorption at these sites\(^14,15\). Further, tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), a critical cytokine in RA pathogenesis, promotes osteoclastogenesis, but is not required for the process of articular bone erosion\(^16\).

Dr. Gravallese then discussed the hypothesis that enhanced bone erosion may be accompanied by a defect in bone formation at sites of articular erosion. The wingless-type/\(\beta\) catenin (Wnt) pathway is required for osteoblast differentiation and function. Wnt proteins are secreted glycoproteins that are critical in skeletal development during embryogenesis, and in organogenesis and tumorogenesis\(^17\). Dr. Gravallese demonstrated the expression of members of the Dickkopf (DKK) family of Wnt signaling antagonists at sites of articular erosion in an animal model of RA. She then discussed 1 study in a TNF transgenic arthritis model of RA, in which articular joint destruction was reversed to a pattern of periarticular bone formation by blockade of DKK1, with no effect on inflammation\(^18\).

Dr. Gravallese concluded that osteoblast maturation and function may be compromised at sites of inflammation, and that Wnt signaling antagonists may contribute to this pathology. Longer term goals are to better understand these mechanisms in order to identify targets for the augmentation of bone formation.

**Upsetting the Balance between Bone Destruction and Formation in Inflammatory Disease.** Georg Schett, MD (University of Erlangen-Nuremberg, Erlangen, Germany) built upon the presentation by Dr. Gravallese with a review of increased systemic bone loss and risk of vertebral fracture in AS and the role of osteoclasts in this process\(^19\). He led a discussion of the enthesopathy of RA versus SpA\(^5\), followed by a discussion of osteitis versus synovitis in peripheral joints\(^8\), saying that osteitis is a hallmark of AS. CD3 T cell aggregates are accompanied by CD20+ B cell aggregates in the bone marrow of patients with AS\(^19\), bone marrow infiltrates drive bone formation\(^20\), and B cells support endosteal bone formation\(^21\). He also discussed the role of sclerostin, an osteocyte-derived molecule, in the bone marrow of patients with AS.

Next, Dr. Schett discussed the sequence of structural damage in AS\(^22\), comparing results from recent studies in AS\(^23,24\). Additionally, he discussed evidence of activated bone morphogenetic protein (BMP) signaling in enthesitis in a mouse model of SpA\(^25,26\). Finally, after referencing Wnt signaling and the DKK1 blockage on modulation of joint architecture, he described the role of matrix metalloproteinase 3 as a predictor of progression in structural damage in AS\(^27\).

**Controlling the Th17 Axis in Inflammatory Disease.** David Fox, MD (University of Michigan, Ann Arbor, MI) briefly reviewed the multiple functions, subsets, and activity of T lymphocytes, then described 2 newer T cell subsets that have critical importance in autoimmunity: CD4-positive (CD4+) regulatory T cells (Treg cells), and CD4+ cells that secrete interleukin 17 [IL-17; T helper 17 (Th17) cells]. Th17, which was recently defined as a distinct Th subset, is a therapeutic target in RA and has a role in SpA and related diseases (inflammatory bowel disease, psoriasis).

Dr. Fox listed the key cytokines in the stages of Th17 development [IL 6 + transforming growth factor-\(\beta\) (TGF-\(\beta\); mouse) or IL-6 + IL-1 (human), IL-21, and IL-23], and said the cells are characterized by specific transcription factors (T-bet for Th1, GATA-3 for Th2, and ROR\(\gamma\)-T for Th17 cells). He described how CCR6-expressing Th17 cells are recruited to inflamed joints via CCL20 in RA and animal models\(^28,29\). Dr. Fox compared Treg versus Th17, saying some cytokines promote both Treg and Th17 (e.g., TGF-\(\beta\)), IL-6 skews differentiation toward Th17 and away from Treg, and that the effects of Treg on Th17 responses are not known. Inducers of Th17 include IL-6, TGF-\(\beta\), IL-21, IL-23, TNF, IL-1, and IL-15. Regulators of Th17 include IL-4, \(\gamma\)-interferon, IL-12, IL-2, IL-35, and interferon-\(\beta\).

After presenting some results relating to IL-17 expression in animal models of arthritis, Dr. Fox returned to several issues regarding human Th17 cells, including the role of TGF-\(\beta\), the duality of Th1 and Th17 cells and their roles in immune-mediated disease, pathogenic versus non-pathogenic Th17 cells, what infections to expect if IL-17 is neutralized, and the multiple Th17 cytokines (IL-17A, IL-17F, IL-22, etc.). In conclusion, Dr. Fox predicted that manipulation of the number and function of Th17 cells will be a central focus in treating immune-mediated disease. The utility of augmenting the number or function of Treg will
benefit from AS treatment46. Early diagnosis of AS/SpA is suppress disease activity and improve functional ability.

APRT1 (aminopeptidase 1), and IL23R (IL-23 receptor) in susceptibility to AS30, and their implications for pathogenesis.

Dr. Colbert discussed the immunobiology of susceptibility genes: HLA-B27, ARTS1, IL23R, and IL1A. HLA-B27 misfolding and activation of the unfolded protein response can lead to increased IL-23 production in an animal model with implications for IL-23 receptor triggering on Th17 T cells3,31,32. Polymorphisms in IL23R are also implicated in susceptibility to psoriasis and inflammatory bowel disease33-35, perhaps by influencing the strength of the Th17 T cell response to IL-23. While proinflammatory functions of IL-1 are well recognized36,37, this cytokine can also promote Th17 development. Understanding the role of ARTS1 (ERAP1) in disease will not be straightforward. It can promote shedding of TNF, IL-6, and IL-1 receptors38, and it is involved in peptide trimming in the endoplasmic reticulum39. This latter activity can alter the peptides presented by class I molecules like HLA-B27 and might also affect its folding efficiency and misfolding. Which activity is more important in AS pathogenesis remains to be determined, and will become an important area of investigation.

Dr. Colbert concluded that the IL-23/IL-17 (Th17) axis may be an important target in AS/SpA40, and noted that preliminary studies have shown that IL-17 is elevated in patients with these diseases41,42.

Epidemiology of AS/SpA. A breakout session was chaired by Muhammad Asim Khan, MD (Case Western Reserve University, Cleveland, OH) and Michael Weisman, MD (Cedars-Sinai Medical Center, Los Angeles, CA). Dr. Khan, summarizing recent population-based epidemiologic data, indicated that AS and related SpA are more prevalent than RA, at least in some countries, such as China and Turkey43,44. Estimated prevalence of AS/SpA in the USA is between 0.35% (excluding undifferentiated SpA) and 1.3%, and that of RA is 0.6%.45. According to a British study, approximately 5% of patients with chronic back pain being seen by primary care physicians may have a mild form of AS that may never progress to definite ankylosis, but who may benefit from AS treatment46. Early diagnosis of AS/SpA is crucial now that more effective therapies are available to suppress disease activity and improve functional ability.

Dr. Weisman discussed the Spondylitis Association of America back pain project, whose goal is to develop a screening tool for inflammatory back pain (IBP) in the medical setting. After a literature review, AS focus groups, and expert advisory board input, the screening tool was tested in 2 case-control studies involving over 600 cases and controls. Dr. Weisman presented the final tool (and scoring algorithm), which was set at 70% sensitivity and 99% specificity where it was determined to have the greatest effect in a chronic back pain population containing approximately 5% subjects with AS. He also briefly reviewed the NHANES I (1971-75) and NHANES II (1976-80) surveys, where prevalence of IBP was approximately 2% in a community setting.

Dr. Weisman then discussed plans for NHANES 2009-10, a US-based, 6-year, SpA-specific survey to provide the first national estimates of IBP, SpA, and HLA-B27 prevalence and subtypes; provide an unbiased population-based genetic study platform for IBP and SpA; define the associations between IBP, HLA-B27, and genetic traits; and develop a valid IBP/SpA screening protocol, which requires accurately redefining the case spectrum of IBP and SpA on a population level rather than a clinical one. Unlike previous arthritis-based NHANES surveys, it will include a detailed pain matrix; additional questions on inflammatory indicators (iritis, heel pain, and psoriasis); SpA body measures (cervical, thoracic, and lumbar spine); genetic testing, and HLA-B27. In preliminary interviews of 248 subjects, response profiles appear to track expectations.

Registries for Spondyloarthritis. A second breakout session was chaired by Atul Deodhar, MD (Oregon Health and Science University, Portland, OR) and John D. Reveille, MD (University of Texas Health Science Center at Houston, TX). Dr. Deodhar discussed the role of patient registries in collecting data on the natural history of SpA, patient outcomes, and the relative safety of treatment modalities. The advantages and limitations of registries were compared with randomized controlled trials and post-marketing studies (Table 1).

Dr. Reveille discussed the Prospective Study of Outcome in AS (PSOAS), an ongoing cohort of > 900 patients with AS followed up to 6 years at Cedars-Sinai Medical Center, University of Texas Health Science Center, National Institutes of Health, and University of California San Francisco, where several factors may help determine outcome in AS (Table 2). Robert Inman, MD (Toronto, Canada) briefly discussed another prospective cohort comprising nearly 400 patients with AS at his institution. Philip Mease, MD (Seattle, WA) reviewed a registry for patients with RA and psoriatic arthritis (CORRONA), with examples of research projects conducted with the longitudinal data. A discussion was held on the pros and cons of starting a new registry versus joining an existing one. Rod Hooker, PhD (University of Texas, Southwestern) discussed a Veterans Administration (VA) based database for patients with AS (PULSAR), suggesting the possibility of merging the VA database and a new SPAR-TAN registry. Rajesh Dixit (Datazoom Solutions Inc., Toronto, Canada) gave a lecture/demonstration on a Web-based AS database that his company developed for the Canadian AS registry (Spondyloarthritis Research Consortium of Canada, SPARCC).

Attendees were invited to form a core group to develop a

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SPARTAN registry, to determine what data to collect, to develop a pilot questionnaire, and to select a software vendor. Funding sources also were discussed. Dr. Deodhar will present the group’s progress at the 2009 SPARTAN meeting.

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 23–25, 2009, in Houston, Texas (see www.spartangroup.org).

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