2007 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; www.spartangroup.org) was founded in 2003 by a group of North American clinicians and researchers to promote 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[1,2]. SPARTAN held its fifth annual research meeting in September 2007 in Cleveland, Ohio. Highlights of the meeting included updates on current research in SpA, including epidemiology and genetics, bone formation and inflammation, biomarkers, activation of the IL-23/IL-17 axis, and animal models. A presentation was made on basic and clinical science of inflammatory bowel disease, and an educational pre-meeting conference was specifically designed for rheumatology fellows. (First Release May 15 2008 J Rheumatol 2008;35:1398–1402)

The fifth annual research meeting of The Spondyloarthritis Research and Therapy Network (SPARTAN) was held in September 2007 in Cleveland, Ohio, USA. Meeting highlights included updates on current research in spondyloarthritis (SpA), including epidemiology and genetics, bone formation and inflammation, biomarkers, activation of the IL-23/IL-17 axis, and animal models. A presentation was made on basic and clinical science of inflammatory bowel disease, and an educational pre-meeting conference was specifically designed for rheumatology fellows.

Epidemiology and genetics of spondyloarthritis

John D. Reveille, MD (University of Texas, Houston Health Science Center), updated the group on the prevalence of AS and related SpA in the US, comparing previously cited rates[3] with the most current projections (between 0.2% and 0.5% for AS, 0.4%–1.3% for SpA)[4]. He also reviewed the results of the National Health and Nutrition Examination Survey (NHANES) I project, a representative study conducted among 6913 participants 25–74 years old at 100 locations in the US between 1971 and 1975 (available at www.cdc.gov/nchs/data/nhanes.htm), from which the higher figure for AS (0.5%, based on the prevalence of grade 3 or 4 sacroiliitis) was calculated.

Dr. Reveille next reviewed the genetic epidemiology of AS, concluding that genetic factors contribute greater than 90% to disease susceptibility[5]. He briefly reviewed the role of HLA-B27, which forms less than 40% of the overall risk for SpA, then discussed the major histocompatibility complex (MHC), which may contribute as much as 50% of that risk. Dr. Reveille described the MHC family, listing several genes implicated in a predisposition to AS [e.g., HLA-B60 (B*4001), HLA-DR1, HLA-DR4][6]. He also mentioned 2 non-MHC genes that have shown some association with AS/SpA: ANKH (ankylosis, progressive homolog), a multipass transmembrane protein, and CYP2D6 (cytochrome P450 2D6), which may promote inflammation via T cells[7,8].

Dr. Reveille discussed recent genomic studies with the group and showed results that genotyped 2 single-nucleotide polymorphisms (SNP), the ARTS1 (otherwise known as ERAAP, or endoplasmic reticulum associated aminopeptidase regulator) and IL-23R, and their association with AS[9]. Within the endoplasmic reticulum, ARTS1 is involved in trimming peptides to the optimal length for MHC Class I presentation; it also cleaves cell-surface receptors for the proinflammatory cytokines IL-1 (IL-1R2), IL-6 (IL-6Rα),

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and TNF (TNFR1), thereby downregulating their signaling. IL-23R is a major gene for Crohn's disease (CD) and possibly for ulcerative colitis (UC) and has a weaker association with psoriasis[9].

The absence of association of ARTS1 with CD or UC, neither of which are HLA Class I-associated but which are closely related clinically to AS, is suggestive that the mechanism of association of ARTS1 with AS is related to its role in peptide presentation or another aspect of the unusual immunobiology of HLA-B27. The association of IL-23R variants with AS raises the possibility of targeted cytokine blockade as a novel treatment, and suggests that Th17 lymphocytes play a major role in AS. Dr. Reveille concluded that these findings confirm previous twin and family segregation data, and suggest the presence of major non-B27 genes in AS; they also suggest that further high density linkage disequilibrium mapping is likely to be fruitful in this disease.

Bone formation and inflammation in spondyloarthritis

Christopher Ritchlin, MD (University of Rochester Medical Center), discussed the pathophysiology of AS, emphasizing that it is primarily a disease of bone and enthesis and not synovium[10]. He reviewed the processes of bone development, remodeling, and bone cell differentiation[11], and outlined the pivotal role of monocyte effector cells in immune-mediated inflammatory disorders (IMID), stating that patients with a particular IMID may have higher numbers of specific monocyte effector cell precursors in their peripheral blood. He then described a study of TNF-induced myelopoiesis in erosive arthritis, suggesting that osteoclast precursors are increased in erosive IMID phenotypes such as rheumatoid and psoriatic arthritis[12]. Of particular interest was the absence of osteoclast precursors in AS, a finding that underscores the local bone resorption that takes place in this disorder compared with the widespread peripheral erosions observed in many patients with RA and PsA.

Dr. Ritchlin next discussed bone marrow edema (BME) in AS, presenting results of recent studies of BME in RA[13] and of bone-cartilage interface and marrow infiltrates in AS[14,15]. In a discussion of hematopoiesis of bone and marrow stromal cells, he described the role of osteoblasts in the development of hematopoietic stem cells in the bone marrow as well as the steps that lead to the differentiation and maturity of osteoblasts[16], which appear to be controlled by Wnt signaling pathways[17]. The Wnt proteins belong to a family of highly conserved secreted signaling molecules that regulate cell-to-cell interactions during embryogenesis and osteoblast differentiation[18]. Dr. Ritchlin also discussed the Dickkopf (DKK) family of proteins as inhibitors of the Wnt pathway; DKK-1 may interfere with osteoblast differentiation and thus with bone formation and homeostasis[19].

Dr. Ritchlin concluded by suggesting that while osteoproliferation in AS may proceed step-wise (i.e., from erosion to fibrotic repair to new bone), it may take place independent of inflammation and erosion. He noted that TNF-α inhibits chondrogenesis and osteogenesis *in vitro*, and that treatment of AS with TNF inhibitors does not appear to inhibit bony progression. He emphasized the importance of identifying patients with early AS, suggesting the need to restore the balance between DKK-1 and Wnt signaling pathway and to identify factors that may lead to increased myelopoiesis. Other potential therapeutic targets include molecules that mediate interactions between osteoblasts and hematopoietic stem cells such as stromal derived growth factor (SDF-1), macrophage-colony stimulating factor (M-CSF), and vascular endothelial growth factor (VEGF).

Biomarkers in spondyloarthritis

Walter Maksymowych, MD (University of Alberta), suggested that the potential prognostic value of biomarkers may be of major importance to the clinician. Radiographic progression in patients with AS is very slow, and only baseline damage is predictive of subsequent progression[20]. A recent study examined a panel of biomarkers reflecting bone and cartilage turnover as potential predictors of radiographic progression[21]. Only serum matrix metalloproteinase 3 (MMP-3) was shown to be a predictor, and this was evident only in those patients with preexisting radiographic damage. However, the risk for damage progression in AS patients with high MMP-3 (> 68 ng/ml) and preexisting radiographic damage (> 10 mSASSS units) was very high (odds ratio = 78)[21]. Of the 15% of AS patients with high MMP-3 and preexisting radiographic damage, two-thirds developed further radiographic progression over 2 years[21].

Of several biomarkers examined to determine whether they reflect burden of disease, MMP-3 demonstrated cross-sectional correlations with acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein)[22]. MMP-3 also has shown correlation with histopathological features of inflammation in knee joints[23]. MMP-3 is increased in patients with concomitant peripheral arthritis even where acute-phase reactants are normal[23]. Several cross-sectional studies have demonstrated correlations between bone markers and measures of disease activity[24,25].

Consistent correlations have been noted between change in MMP-3, IL-6, VEGF, CTX-II, and bone formation markers with changes in clinical and laboratory indices of disease activity in patients receiving anti-TNF therapies in studies that also examined the degree to which biomarkers reflect treatment response and predict clinical response[22,23,26-28]. Bone formation markers consistently increase with anti-TNF therapies, but no influence has been observed on bone resorption markers[29].

Dr. Maksymowych concluded by listing additional candidate biomarkers for assessment of disease activity and prognosis, including those that regulate bone turnover and remodeling [bone morphogenetic protein 1 (BMP-1), Wnt

protein, DKK-1, and insulin-like growth factor-I [IGF-I)], as well as certain interleukins (IL-17/IL-23) recently implicated in AS inflammation[30].

Activation of the IL-23/IL-17 axis in experimental spondyloarthritis

Robert A. Colbert, MD, PhD (Cincinnati Children's Hospital Medical Center), briefly reviewed the role of HLA-B27 in AS and SpA; he observed that while HLA-B27 may account for 40% of the genetic risk for these complex diseases, several other genes are involved in determining susceptibility and phenotype. After reviewing the class I structure and recognition of HLA-B27, Dr. Colbert discussed misfolding of the protein and its consequences: misfolding may be due in part to slow heavy-chain folding as a consequence of the Glu45 and the unpaired Cys67[31] and the entire HLA-B27 B pocket dramatically reduces peptide loading efficiency[32].

Dr. Colbert next discussed the implications of misfolding of HLA-B27 on inflammation in AS. In transgenic rats, HLA-B27 misfolding is associated with activation of the unfolded protein response (UPR)[33]. UPR activation is prominent when HLA-B27 is upregulated, which appears to exacerbate misfolding[34]. This UPR activation results in increased production of certain cytokines (IFN-ß, IL-23p19) in response to toll-like receptor (TLR) agonists such as lipopolysaccharide. Additional preliminary data revealed that IL-17 is overexpressed in the colon of transgenic rats. Thus, it appears that the IL-23/IL-17 axis is highly activated in this animal model of SpA.

Dr. Colbert discussed how these findings relate to recent studies in HLA-B27-associated human disease. IL-23 receptor (IL-23R) polymorphisms appear to contribute to susceptibility to AS[9], and serum IL-17 appears to be elevated in patients with undifferentiated SpA and reactive arthritis[35]. In addition, evidence of UPR activation in synovial fluid mononuclear cells from patients with SpA has been published[36]. Together, these studies implicate the IL-23/IL-17 axis as being involved in the pathogenesis of SpA, and are consistent with a role for HLA-B27 misfolding in activating this pathway.

Animal models of spondyloarthritis: Inflammation and remodeling

Rik Lories, MD, PhD (Katholieke Universiteit), began with emphasizing the need to better understand the mechanism of ankylosis in SpA. The phenotypical appearance of different types of arthritis can be used to understand tissue responses in the joint and define subtypes such as destructive and remodeling arthritis[37,38].

Dr. Lories then discussed recent observations of spontaneous occurrence of arthritis in aging male DBA/1 mice as a model for SpA and PsA[39,40]. After showing slides of entheseal cartilage and bone formation, he concluded that this is a very interesting model to study molecular aspects of joint ankylosis; however, like any model of human disease there are also limitations, e.g., no axial disease was observed, there was no HLA-B27 association, and inflammatory aspects are still unclear.

Dr. Lories next discussed bone morphogenetic proteins (BMP), which are present in the process of ankylosing enthesitis, and he presented results of BMP inhibition in mice[41-43]. He concluded that BMP signaling is an important molecular pathway in the pathological cascade of ankylosing enthesitis, and that gene transfer of noggin, a BMP antagonist, interferes with early stages of ankylosing enthesitis.

Dr. Lories briefly discussed the potential involvement of Wnt signaling in ankylosing enthesitis and the links between inflammation and ankylosis. He reminded the group that entheseal cartilage and bone formation leading to ankylosis is a hallmark of SpA, but that while inflammation and ankylosis may be linked, they are largely independent processes. He presented recent results showing that inhibition of TNF does not affect joint ankylosis in a mouse model of SpA[44]. He concluded that control of inflammation does not mean control of the disease and suggested that new tissue formation should be a therapeutic target.

Inflammatory bowel diseases 2007: A model disease for merging basic, translational, and clinical science

Stephan R. Targan, MD (Cedars-Sinai Medical Center), reviewed the etiologic theories in inflammatory bowel disease (IBD), stating the importance of 3 factors: genetic predisposition to IBD; immunoregulatory defects that result in abnormalities in the mucosal immune system (e.g., over- or under-production of inflammatory or regulatory cytokines); and an environmental triggering event — most notably, the role of the commensal enteric microbial flora. Historical research with many animal models of IBD identified the first CD-susceptibility gene as NOD2/CARD15, an intracellular innate immune sensor for microbial products that may play an important antibacterial role in the gut. He described several cells critical for host defense against enteric microbes: intestinal epithelial cells, macrophages, and dendritic cells.

Through the recent technology of genome-wide association (GWA), more rapid identification and linkage of specific genes to IBD and CD can be accomplished. Dr. Targan then reviewed the association between IL-23R, IL-17A, and IL-17RA and their susceptibility to CD and he summarized the synergistic effects of IL-23R and IL-17A in IBD[45,46].

Dr. Targan next discussed the presence of antibodies in IBD and the association of antibody responses to microbial antigens and complications of CD[47-50]. He summarized the independent associations between 4 CD-associated antibodies (anti-I2, ASCA, anti-CBir1, and anti-OmpC) and NOD2 with several CD phenotypes [small bowel (SB) disease,

fibrostenosis, internal perforating phenotype, and SB surgery][51]. He briefly discussed the TNF superfamily; specifically, TL1A (TNFSF15) has been found to be a CD-susceptibility gene[52,53].

Dr. Targan suggested that in the near future, analyses of an IBD panel (serotype, genotype, proteotype, phenotype) may identify a specific IBD subtype for each patient, which in turn could aid in disease prognosis and patient subset-specific therapies.

Highlights of fellows' meeting

Twenty-two 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 "Genetics and pathogenesis of SpA" (David Yu, MD), "Early diagnosis of SpA" (Michael Weisman, MD), "Extra-articular features of SpA" (Daniel Clegg, MD), "Related SpA phenotypes: psoriatic arthritis" (Allen Anandarajah, MD), "NSAID and biologics in the treatment of AS: concepts and controversies" (Walter Maksymowych, MD), and a metrology and patient-centered exercise that included patient perspectives, examination, and metrology (Drs. Allen Anandarajah, Daniel Clegg, M. Asim Khan, Walter Maksymowych, Michael Weisman, and David Yu; Dr. Khan provided 4 patients for this exercise).

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 25–26, 2008, in Cleveland, Ohio (see www.spartangroup.org).

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