SPARTAN

Spondyloarthritis Research and Treatment Network

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Greetings!

SPARTAN continues to grow its impact through expanded membership and exciting new projects. In May we conducted another successful annual meeting and want to thank everyone who organized and participated in the event. This newsletter will summarize the highlights from the meeting and updates about ongoing educational events and studies including CLASSIC.

Respectfully,

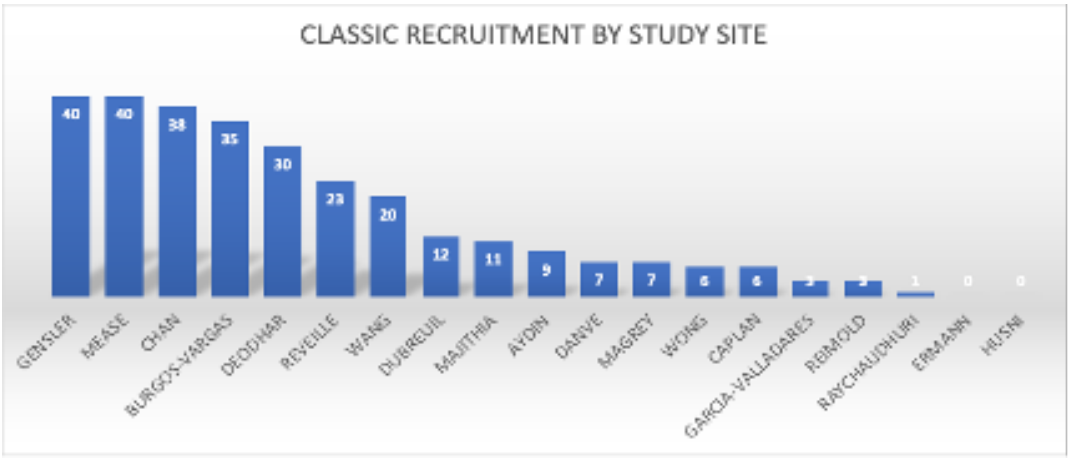
Judy

Judith A. Smith, MD, PhD
SPARTAN Chair

SPARTAN PROJECTS

CLASSIC STUDY

The past quarter has seen exciting recruitment trends! At this time, 19 sites have been activated and three more pending test imaging approval. Three sites have completed their recruitment goal and five more sites are close to completion. In total, 281 individuals have been recruited into CLASSIC.



SPARTAN REFERRAL RECOMMENDATIONS

Over the next two years, a team led by Drs. Abhijeet Danve, Maureen Dubreuil, and Atul Deodhar will develop SPARTAN recommendations for referral to rheumatologists of patients with chronic back pain who may have axSpA. Their goals will be to develop recommendations for non-rheumatologist clinicians as well as self-referral by persons with chronic back pain. Their first objective, just underway, is asking PICO

questions of stakeholders and conducting a systematic review to develop discrete choice experiments.

NON-RHEUMATOLOGY HCP EDUCATION PROJECT – EARLY IDENTIFICATION AND DIAGNOSIS OF AxSpA (EIDA)

With funding through a Pfizer Global Medical Grant, SPARTAN is organizing a working group to execute the EIDA education project. The primary objective of this project is to educate non-rheumatology HCPs about clinical features that suggest the presence of axSpA and should prompt consideration of referral to a rheumatologist. A secondary but equally important objective of this project is to build relationships between axSpA experts (SPARTAN members) and non-rheumatology HCPs that will lead to enduring benefits beyond the limited duration of this program.

SPARTAN BIOREPOSITORY

SPARTAN has assembled a working group to develop a biorepository of well-characterized individuals with axSpA and design a biomarker study alongside the registry. Membership updates will continue as the project unfolds.

HIGHLIGHTS FROM THE ANNUAL MEETING

SPARTAN Spondyloarthritis Research and Treatment Network

19th ANNUAL MEETING
MAY 20–21 · All Virtual

Congratulations to Joel Taurog, MD, on being honored with the Research Career Achievement Award. Dr. Taurog's investigations into the HLA B27 gene have been foundational to our field.

Session Reviews

by Dr. Jean Liew

The keynote lecture was delivered by Dr. Robert Colbert of NIH/NIAMS and was entitled Does HLA-B27 Affect Bone Formation and Mineralization?

He delved into the question of whether mesenchymal stem cells (MSCs) were bystanders or active participants in new bone formation. An important finding to note here was that HLA-B27 expression was

necessary and sufficient for increase bone mineralization.
He then turned his focus onto IL-1α and IL-1β, cytokines that are responsible for increased mineralization, and which are produced by MSCs. PGE2 production is also implicated in bone mineralization and is found to be differential in SpA (higher) vs healthy controls.
This led to the working model of new bone formation in which MSCs produce IL-1α and in an autocrine/paracrine fashion, induces PGE2 production. This leads to increased bone mineralization via osteoblasts.

Oral abstracts from trainees

Yuliya Afinogenova, MD (Yale University), mentor Abhijeet Danve MD: Self-referral Strategy for Early Diagnosis of Axial Spondyloarthritis-Preliminary Analysis from Finding Axial Spondyloarthritis Study. She described a pilot referral study using a newly developed set of screening questions ("A-tool") for non-rheumatology referrals as well as patient self-referrals through the electronic medical record and Facebook.

Adam Lefferts, PhD Candidate (University of Colorado), mentor Kristi Kuhn, MD, PhD: Gut Derived T cells are Cytokine Competent and Contribute to Inflammation in the Joint. His work on the gut-joint hypothesis focusing on intra-epithelial lymphocytes (IELs), which are a T-cell subset involved in maintaining barrier homeostasis, and which have heightened TNF competence. They were able demonstrate a direct link between the gut and joint through trafficking of gut-derived T cells, which have the potential to be directly pathogenic through the production of pro-inflammatory cytokines like IL-17 and TNF, leading to exacerbation of joint inflammation.

Maricela Haghiac, PhD (MetroHealth Medical Center), mentor Marina Magrey, MD: Integrative Analysis of mRNAs to Identify Sex Differences in Th-17 Mediated Inflammation in Ankylosing Spondylitis. They obtained PBMCs from 10 female and 10 male participants with AS. After obtaining IL-17 enriched cells, they extracted total RNA and identified changes in mRNA expression using next generation RNA-sequencing. They found that multiple cytokine genes were dysregulated between men and women with AS; of note IL23R and IL-6R genes were downregulated in men.

Seed Grants for Junior Faculty

Shao-Hsien Liu, PhD, MPH (University of Massachusetts): The Interplay between Gender and Sex in Understanding Health Quality of Life among Patients with Axial Spondyloarthritis: an Exploratory Sequential Mixed Method Study. He used data from two studies (NHANES and SPA-SED) to look at individuals meeting the Amor-IBP criteria (n~200) and how many days per the last 30 that they reported feeling physically or mentally unwell. He also brought in qualitative interview data on health-related quality of life and how that may differ by gender.

Jean Liew, MD (Boston University): The Impact of Tumor Necrosis Factor Inhibitor Use On Cardiovascular Events In Ankylosing Spondylitis. Using PSOAS, a prospective AS cohort, there was no evidence to support an increased riskof incident hypertension with TNFi use, after accounting for important baseline and time-dependent confounding factors.

Fellowship Grants for Pilot Projects

Yuliya Afinogenova, MD (Yale University); mentor Abhijeet Danve, MD: Awareness and Attitudes Regarding Axial Spondyloarthritis among Non-Rheumatology Providers

She presented the results of a survey for primary care providers and their understanding of inflammatory back pain. The majority of PCPs (n=138 respondents) reported that they did not regularly assess for the presence of IBP, and a plurality were not comfortable with making an IBP diagnosis. This brought up an interesting discussion about potential educational interventions for PCPs, and how this might impact the lengthy diagnostic delay in axSpA.

Pamela Diaz, MD (University of Toronto); mentor Lihi Eder, MD, PhD: Axial Psoriatic Arthritis Correlation between Clinical, Genetic and Axial MRI Findings. The overall goal of the study was to characterize axial PsA using whole-spine MRI and to correlate imaging features on MRI with clinical and genetic data. As part of one aim, they performed whole spine MRI in patients with active PsA patients about to initiate systemic therapy in order to assess the correlations with IBP (by 3 different criteria), and with the ASAS classification criteria for axSpA. Overall, there was a low agreement between axSpA ASAS classification criteria and the presence of MRI-Spondylitis; as well as low agreement between the different IBP criteria with MRI-Spondylitis.

Rouhin Sen, MD (University of Colorado), mentor Liron Caplan, MD, PhD: A Tough Cell: the Argument for a Biomarker of Clinical and Imaging Outcomes in Spondyloarthritis as a Biomarker in Axial Spondyloarthritis. Using VA data from the Corporate Data Warehouse (CDW) and PULSAR, they looked at the neutrophil/lymphocyte ratio and the platelet/lymphocyte ratio as potential biomarkers for AS patients. It would be interesting to see whether these ratios would be better biomarkers for disease activity than CRP.

Year in Review – Part 1

By Dr. Michael Weisman

The Year in Review session highlighted recently conducted impactful research. First, Dr. Bridget Wang reviewed the following study:

Feld J et al. Is axial psoriatic arthritis distinct from ankylosing spondylitis with and without concomitant psoriasis? Rheumatology (Oxford). 2020 Jun 1;59(6):1340-1346.

The very productive Toronto group asks the question – despite considerable clinical overlaps, are there true phenotypic differences between ankylosing spondylitis (AS) patients (with and without psoriasis) compared to those with psoriatic arthritis (PsA) possessing axial disease? They cite prior studies that appear to show differences (axial PsA develops later, less associated with HLA-B27, etc.) but these studies, in their opinion, have limitations due to case selection and cross-sectional design. The value that Toronto brings to the table is that they have a set-up based on two longitudinally designed research cohorts, each followed over many years, and created from the outset focused on the primary research interests of two different groups of investigators – AS based on modified New York AS criteria, and PsA (with peripheral or axial manifestations) in the presence of psoriasis. Each cohort is staffed separately by either SpA experts or AS experts. The AS cohort consisted of AS with psoriasis and AS without (AS defined by modified NY criteria), and the PsA cohort consisted of those with sacroiliitis (grade 2 or higher NY criteria) and those with PsA and exclusively peripheral disease. The main result was that patients with pure AS were quite different phenotypically and remained so over time,

whether or not they had psoriasis; their work supports the hypothesis that AS and axial PsA are different disease entities and not merely part of the same spectrum. What have we learned from Toronto, and what does this tell us about the biology? Remember, the Toronto group only defined axial disease based on pelvis radiographs, and not on findings in the lumbar spine. If one reviews the landmark article from Currier McEwen (A&R; 14: May-June 1971) where they observed that the radiographic appearance of syndesmophytes in the entire spine differed (in location and associations) between AS and AS with psoriasis, you might find something different. In fact, some patients with psoriasis only have syndesmophytes and no sacroiliac disease! Does spinal bone formation occur in psoriasis via a different (and a potentially genetically induced) mechanism? What is the impact of mechano-transduction on the spine if you are a certain age or have psoriasis or HLA-B27? As usual, more questions than answers, but the differences persist. The Toronto group did a nice job, but there is more to axial disease than just seen in the pelvis, and maybe this will be their next study.

Next, in the Year in Review Session, Dr. Lianne Gensler discussed:
Molto A et al. Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomized TICOSPA trial. Ann Rheum Dis. 2021 May 6.

The ASAS group from three European centers (France, Belgium, Netherlands) asked the question - do the 2017 ASAS/EULAR guidelines for the management of axial SpA provide an advantage over usual care? They decided to perform a study such that if these guidelines were followed to the hilt in a treat-to-target design, can we see an advantage (or not) compared to usual care? Utilizing a cluster design (each center was randomized, rather than patients themselves) in bio-naïve patients, the primary endpoint was selected not on a disease activity model, but on a model where the choice for a target was a health index that included functional assessment and patient-reported outcomes. The reported results indicated that this was a negative study; treat to target was not different from usual care. The authors propose two reasons for their non-statistically significant results. One reason was the choice of a target - they deliberatively chose a "high-bar" measure and not one that was disease activity related. The second

reason was the presence of an unusually high response in the usual care group. It is likely that they were close to the real reasons, but they didn't quite get it right in either case. If you go back to read the original (positive) treat to target study, or TICORA, where intensive management was compared to usual care, the investigators there chose non-biological usual care drugs (the triple therapy group) to treat RA. These agents are marginally effective if used alone. However, if they combined them in an aggressive strategy where decisions for escalation were made by clinic staff based on measurements that were taken out of the hands of doctors, then they might show a difference, which they did. In that case it was the strategy, and not the drugs or the doctors, that made up the difference. Finally, and related to the above comments, it was likely the choice of expert SpA clinicians to implement either the escalation strategies or usual care approaches employing biologic drugs that provided the (so called "unexpectedly") favorable results in the usual care arm of the study. It appears that biological drugs to treat axial SpA are so effective in the hands of SpA experts that it didn't matter what the target was, or how they were used. It's not clear that we learned very much from this study as it was designed.

Top Spondyloarthritis Publications 2020*

*Based on number of citations

Shotgun metagenomics reveals an enrichment of potentially cross-reactive bacterial epitopes in ankylosing spondylitis patients, as well as the effects of TNFi therapy upon microbiome composition
Annals of Rheumatic Disease 2020 Jan;79(1):132-140.

Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: Results from a 48-week phase IIb, randomised, double-blind, placebo-controlled, dose-ranging study
Annals Rheum Disease 2020 May;79(5):595-604.

Anti-TNF treatment during pregnancy and birth outcomes: A population-based study from Denmark, Finland, and Sweden.
Pharmacoepidemiology Drug Safety 2020 Mar;29(3):316-327.

Serum calprotectin: A promising biomarker in rheumatoid arthritis and axial spondyloarthritis
Arthritis research and Therapy 2020 May;22(1):105

Altered Cytotoxicity Profile of CD8+ T Cells in Ankylosing Spondylitis.
Arthritis and Rheumatology 2020 March; 72(3):428-434

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NEWS AND EVENTS

The 12th International Congress on Spondylarthritides, Ghent, Belgium (HYBRID)
September 9-11, 2021

ACR CONVERGENCE (VIRTUAL)
November 3-5: Global Rheumatology Summit, Basic and Clinical Research Conference, and Radiology Bootcamp
November 5-9 ACR Convergence scientific programming and special events
November 10: ACR Review Course
November 10: SPARTAN GRAPPA ASAS Symposium on AxSpA and PsA

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SPARTAN
PO Box 55491
Portland, OR 97238
lisa@spartangroup.org | www.spartangroup.org