Proceedings of the 2015 AASOG conference:
Reducing disparities in sarcoidosis through personalized care and increased detection

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Abstract. The 2015 annual meeting of the Americas Association of Sarcoidosis and Other Granulomatous Disorders (AASOG) was held on September 25th and 26th at the University of Colorado Anschutz Medical Campus in Aurora, CO, U.S.A. The meeting was hosted by National Jewish Health and the theme of the meeting was "Reducing Disparities in Sarcoidosis through Personalized Care and Increased Detection". The meeting was endorsed by the American Thoracic Society (ATS) and the Foundation for Sarcoidosis Research (FSR), and was conducted through support provided by the National Institutes of Health (NIH), particularly the National Heart Lung and Blood Institute (NHLBI), and an unrestricted educational grant from Mallinckrodt, Inc. The meeting participants were predominantly from North America, and included preeminent experts and emerging clinical scientists engaged in sarcoidosis research. The AASOG meeting was held in parallel with a sarcoidosis patient conference that was organized and funded by the Foundation of Sarcoidosis Research (FSR). The AASOG talks covered various state-of-the-arts topics related to sarcoidosis research and care; most notable were talks focusing on preliminary and emerging data from the Genomic Research in Alpha-1 antitrypsin Deficiency and Sarcoidosis (GRADS) study, recent novel immunological and genomic discoveries that further our understanding of sarcoidosis disease pathogenesis, results from clinical trials in sarcoidosis and proposals of novel therapeutic targets for the treatment of sarcoidosis, the introduction of the FSR sponsored clinical studies network, insights from other granulomatous diseases, and a focus on extra-pulmonary sarcoidosis, particularly cardiac disease, small fiber neuropathy, and fatigue. A session dedicated to scientific abstracts from predominantly junior investigators and five oral abstract presentations brought the conference to a conclusion. A brief overview and selected excerpts of the 2015 AASOG meeting proceedings are provided herein. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 264-268)*

The changing landscape of sarcoidosis

Sarcoidosis is a multi-system, T-helper 1 (Th1) cell biased granulomatous disorder that develops in genetically predisposed individuals who are exposed to yet unknown environmental trigger(s) acting as an antigen (1). The etiology of various organ manifestations, variable disease severity and disease course remains unknown and the differences in disease prevalence, severity and course among various ethnic groups is also incompletely understood. Multiple factors, known and unknown, play a role in the health disparities in sarcoidosis including genetic predisposition (2), occupational and environmental exposures, socioeconomic status and access to care

(3). After opening remarks from the host, the conference commenced with a plenary talk to set the stage for the conference, "The changing landscape of sarcoidosis" presented by Dr. David Moller from Johns Hopkins University. Dr. Moller argued for deviating from solely conducting hypothesis testing to including hypothesis generating studies to make large advances in understanding sarcoidosis pathology. The role of "big science" to fill the gaps of knowledge in environmental factors in sarcoidosis was emphasized, as well as on the need to explore and develop biomarkers for early detection of disease, disease course and treatment response. By using molecular phenotyping over clinical phenotyping to identify sub-phenotypes, Dr. Moller noted that we could enhance prediction of sarcoidosis clinical course and treatment responses. Calling out the need to identify "Centers of Excellence" and to study their approach to optimize sarcoidosis management, Dr. Moller proposed that this could lead to enhanced outcomes to identify approaches that can be applied across other centers and clinics and enhance the care of patients with sarcoidosis across the US and internationally. Finally, Dr. Moller encouraged a new focus on the prevention of progressive disease and improving disparate health outcomes by focusing on the points above.

Advances in immunopathology

Sarcoidosis has traditionally been considered a Th1 biased disease driven by IFN-γ (1) although recent findings implicate other arms of the immune system and a more nuanced understanding of the Th1 process in the pathology of sarcoidosis (4-6). Several talks focused on novel findings in the immunopathology of sarcoidosis. Initiating these sessions, Charlene Hawkins, PhD from Vanderbilt University Medical Center presented their recent work on the impact of multiple dysfunctional immune parameters on the pathogenesis of sarcoidosis including reduced CTLA-4 expression on T-regs and Th17 cells and evidence of T-cell exhaustion as a contributor to disease pathogenesis (7). Laura Koth, MD from the University of California San Francisco presented novel findings on the potential role of Th17 cells in sarcoidosis immunopathogenesis. Though the role of Th17 cells in sarcoidosis is not fully characterized,

they may have been misclassified in prior studies as Th1 due to their ability to produce IFN-γ. By identifying T-cells by their chemokine receptors, Dr. Koth and colleagues were able to accurately distinguish T helper subsets. The Th17.1 subset was shown to be the predominant subset in the lungs of sarcoidosis patients (6). These findings challenge the current beliefs of the pathogenic cell in sarcoidosis and create new implications for future mechanistic studies, immunophenotyping of disease and treatment modalities.

Wonder Drake, MD from Vanderbilt University Medical Center discussed immunologic indicators of clinical outcome, focusing on the concept of T-cell exhaustion and restoration of Th1 cytokine expression following clinical resolution (7). As an example of immune dysregulation in sarcoidosis, Dr. Drake discussed the role of PD-1 in sarcoidosis patients with progressive disease, noting that they have increased expression of PD-1 on CD4+ cells in PBMC and proposing a role for anti-PD1 therapy in sarcoidosis (8). Advancing the translation of immune mechanisms to therapy, Kevin Gibson, MD discussed potential therapeutic targets in sarcoidosis based on research investigating T-cell signaling, Th1, Th17, and P38 MAPK in sarcoidosis. He summarized several biologics under development for inflammatory diseases for future exploration as targets in sarcoidosis including T-cell activation (CTLA-4, VIP), Th1 cytokines (IL-6, IL-12p40), Th17 (IL-17, IL-23), cell recruitment and signal transduction pathways. A major struggle in the field of sarcoidosis has been the lack of quality diagnostic and prognostic biomarkers. Edward Chen, MD from Johns Hopkins University pointed out that many of the current biomarkers are not sarcoidosis specific but rely on the non-specific assessment of the inflammation in sarcoidosis. Dr. Chen proposed that serum amyloid A (SAA) may be a potential new biomarker for sarcoidosis, suggesting a link between candidate microbial triggers and chronic disease that results from the local accumulation of SAA following immune control of an infectious agent (9). To help care of patients with diverse organ involvement, Dr. Chen proposed the consideration of a biomarker panel for sarcoidosis.

Preliminary data from Genomic Research in Alpha-1-Antitrypsin Deficiency and Sarcoidosis (GRADS)

After a successful year and a half of recruiting for the NIH-sponsored (GRADS) project, preliminary data is starting to emerge. Dr. Koth shared some exciting preliminary data from GRADS, on behalf of the studies' Principal Investigators and multiple sites involved. Much of the initial work presented questioned whether peripheral blood gene expression could be utilized to distinguish sarcoidosis from other diseases, identify genes related to pathology and prediction of clinical course. Initial findings reveal that sarcoidosis gene expression does have a "robust signature" that helps distinguish sarcoidosis from healthy controls as well as other relevant diseases such as mycobacterium tuberculosis. Gene expression in both blood and lung had complementary up-regulation of interferon signaling genes which is consistent with the common notion that sarcoidosis is an IFN-γ mediated disease. Dr. Koth presented her findings on the transcriptional marker *CXCL9* which was found to have predictive properties of progressive disease (10). One of the aims of the GRADS study was to study the lung microbiome of sarcoidosis patients and its potential association with disease phenotype. Alison Morris, MD, MS director of the University of Pittsburgh HIV Lung Research Center presented the preliminary microbiome findings from GRADS but the full analysis is still ongoing and needs to be completed and integrated with the clinical data before any deductions can be made from these findings.

Advancing clinical care of sarcoidosis

With present data demonstrating the rise in sarcoidosis related mortality and morbidity, advancements in clinical care need to be at the forefront for this disease. Marc Judson, MD from Albany Medical College reported on the "path forward" in clinical trials, and highlighted the need to determine what we are trying to study to help develop appropriate endpoints of clinical trials. Specifically, we need to be able to determine if our interventions have anti-granulomatous activity or physiological benefit, improve organ function, or improve the quality of life of

the patient and based on these goals, utilize the most specific and relevant clinical outcomes. D. Judson emphasized that there should be a focus on identification of corticosteroid sparing agents, exploration of drug side effect profiles, and inclusion of fibrotic outcomes and treatments to reduce fibrosis in future studies.

Recently, the Foundation for Sarcoidosis Research formed a Clinical Studies Network (FSR-CSN) to address simple clinical questions and serve as a platform for collaborative research efforts amongst researchers and pharmaceutical companies. Daniel Culver, DO from The Cleveland Clinic Foundation discussed the first CSN trial, a combination of an observational study about patient reported outcomes and burden of disease. As part of this multicenter study, each CSN site will be responsible for enrolling patients who will complete monthly electronic assessments with the plan to analyze the trajectory of measured on-line sarcoidosis assessment platform (OSAP) items. The goal of this study is to ensure that the use of established sarcoidosis phenotypes of severity accurately reflect patient concerns, function and employment, and screen the patient's perspective of their course of disease. As secondary outcomes, the study will also evaluate current tools used to assess sarcoidosis disease status, including the minimal clinically important difference (MCID) of the King's sarcoidosis questionnaire (KSQ) and compare the results of the KSQ and sarcoidosis assessment tool (SAT). The study will hopefully expose the relation of patient reported outcomes to current phenotypes and endpoints and burden of disease and allow better refinement of phenotypes and define future tools for the conduct of clinical trials and studies in sarcoidosis.

Lessons learned for sarcoidosis from other granulomatous diseases

Looking to other granulomatous diseases may provide valuable insights into new approaches and ultimately discoveries in sarcoidosis. This conference was fortunate to have distinguished speakers from outside the sarcoidosis realm. Dr. Thomas Wynn from the National Institute of Allergy and Infectious Diseases – National Institute of Health (NIAID) was the keynote speaker and discussed the mechanisms of fibrosis in chronic granulomatous inflam-

mation and the contribution of the type-2 response in the initiation, maintenance, and resolution of fibrosis in a schistosomiasis model of fibrotic disease. Dr. Andrew Fontenot from the University of Colorado reviewed his laboratory's work on the mechanism of HLA Class II and T-cell responses in chronic beryllium disease, a granulomatous lung disease that mimics sarcoidosis but with a known antigen, beryllium. Dr. Matyas Sandor from the University of Wisconsin discussed the role of granuloma induced vascular endothelial growth factor (VEGF) in inducing lymphangiogenesis during granulomatous infections and the potential role of VEGF and its ligand, VEGF-3, in the pathogenesis of granulomatous lung disease. Dr. Tasha Fingerlin from National Jewish Health discussed the findings in idiopathic pulmonary fibrosis as an example of how advancing discoveries from genetic research can impact the clinical care of patients. These talks all highlighted the importance of looking outside the works of sarcoidosis researchers, to consider mechanisms and approaches identified and used in other similar but distinct diseases.

ADVANCES IN EXTRA-PULMONARY SARCOIDOSIS

While pulmonary sarcoidosis continues to result in the greatest organ specific morbidity and mortality in the US, the impact of other organ impairment is significant and appears to be growing (Would add the reference from Finnish Cardiac sarc). Dr. Karen Patterson from the University of Pennsylvania discussed the current challenges and gaps in knowledge in extra-pulmonary sarcoidosis. Cardiac sarcoidosis (CS) is a potentially lethal complication of sarcoidosis that is difficult to detect and for which there is a great need to develop biomarkers that can assist in the evaluation and management of CS patients. Dr. Elliot Crouser from Ohio State University, Thomas Schindler, MD from Johns Hopkins University, and Matthew Zipse, MD from the University of Colorado each discussed biomarkers for cardiac sarcoidosis using exosomes, imaging, and electrical biomarkers, respectively. A summary by Dr. Crouser of the inflammatory biomarkers of CS, such as serum angiotensin converting enzyme (ACE), Urine 8-OHdG, Lymphopenia, IL-10 and Chitotriosidase highlighted the non-specific nature of these markers for a specific organ and the

need for more organ and disease specific biomarkers. The cardiac specific biomarker, troponin, appears to associate with disease activity but has a low sensitivity for sarcoidosis. Dr. Crouser reported on an active pilot study utilizing exosomes from plasma samples by next generation sequencing (NGS) to uncover unique transcripts for CS. Dr. Schindler presented several challenging clinical cases, where the use of the cardiac 18-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging protocol was utilized to interpret and diagnose the case. CS has been shown to have high prevalence of electrophysiological manifestations, including atrioventricular blocks (AVB), atrial arrhythmias, ventricular arrhythmias, and sudden cardiac death. To this end, Dr. Zipse emphasized the important role of electrophysiologists in the assessment and management of CS and as essential members of the multidisciplinary medical team caring for patients with CS. As CS has been proven to be under-recognized in prior studies and can result in sudden death, Dr. Zipse proposed that possible electrical biomarkers may be utilized to help improve screening and diagnosis. Dr. Zipse reiterated that CS should be considered any time a patient with extra cardiac sarcoidosis presents with (1) AVB at a young age, (2) ventricular tachycaria of unknown etiology or substance, or (3) arrhythmogenic right ventricular cardiomyopathy.

In addition to CS, neurological and psychological manifestations of sarcoidosis are common and have a strong influence on an individual's quality of life. A multitude of neurological symptoms, including: fatigue, impaired concentration, and neurosensory pain, can arise as an indirect consequence of systemic granulomatous inflammation. Dr. Jinny Tavee, a neurologist at the Cleveland Clinic Foundation provided an update on the clinical manifestations, modes of detection, and experimental treatments, including results from a phase 2b clinical trial for small fiber neuropathy (SFN) utilizing ARA290, an erythropoietin like compound under investigation as a therapeutic for SFN in sarcoidosis. Dr. Benzi Kluger, from the University of Colorado, outlined a potential path for fatigue research. A common symptom of sarcoidosis, fatigue is an imprecise terminology with inconsistent measurement rendering many challenges with its research. Dr. Kluger's talk provided tools for measuring perception of fatigues, including; Fatigue Severity Scale and Multidimensional

Fatigue Index, compared to fatigability, including: prolonged muscle contraction, motor tasks, or cognitive tasks with using of physiological measures of electromyography or nerve conduction studies. The use of multiple measures to relate the perception of fatigue to physiology could help provide the distinction between state and trait fatigue and help better define and ultimately treat this pervasive problem.

Conclusion

The 2015 AASOG meeting was brought to a conclusion with a summary of the presentations and a roadmap for future research in sarcoidosis that was presented by Dr. Lisa Maier, incoming president of AASOG. We look forward to the 2017 AASOG meeting in Hershey, Pennsylvania on April 7th and 8th.

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