Key management considerations in sarcoidosis from the American Thoracic Society 2016 Conference

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"The Sword of Damocles" is a story that resonates with sarcoidosis patients. It illustrates the sense of forecasting danger and worsening of their health in an unpredictable fashion. Fatigue, which is a major impediment to their quality of life, also contributes to their stress as family, friends and co-workers believe that these patients are feigning their illness, as they appear "normal." A lingering question for many with sarcoidosis is how they developed the disease.

Sarcoidosis develops in genetically pre-determined hosts who are exposed to complex inorganic or organic antigens that trigger an exaggerated inflammatory immune response leading to granuloma formation. What remains a mystery is whether an infection (e.g., *Mycobacterium tuberculosis* transcriptomes, *Propionibacterium acnes* infection) or a hyper-stimulated immune response to remnant microbial antigens is the initial trigger to the cascade to develop sarcoidosis.

A hallmark feature in the immunological response in sarcoidosis is the presence of CD4+ T cells that interact with antigen-presenting complexes to instigate granuloma formation within tissues.

Certain functional mediators have also been identified in the activation, coordination and amplification of the local and systemic inflammatory response. These functional mediators include chemokines (TNF-alpha, IFN-gamma, IL-12, IL-18, STAT 1, TBET), lymphokines, innate (macrophages, neutrophils, eosinophils and mast cells) and humoral immunity (B-cells, antibodies and circulating immune complexes). Less certain is the role of Th-17 cells. Th-17 and Th-17.1 responses may be upregulated in sarcoid, whereas, T-regulatory cells (CD4:CD25$_{bright}$ lymphocytes) are the major contributing factor for the down-regulation of sarcoidosis cell-mediated immune response. Having high T-regulatory cells present bodes a good prognosis in sarcoidosis.

The question of whether autoimmunity can drive chronic sarcoidosis has been raised. Some patients have elevated ANA or rheumatoid factor, but there is lack of a specific panel of autoantibodies that help diagnose sarcoidosis. As in other chronic inflammatory conditions, amyloidosis may ensue. Chen *et al*. have shown serum amyloid A (SAA) to be both a structural component of the non-caseating granuloma formation and an effector of the innate-immunological response system regulating the degree of granulomatous inflammation in sarcoidosis (1,2).

Clinical monitoring and therapeutic intervention is largely based on symptoms. Discordances between patient symptoms from radiographic appearance and physiological parameters is not uncommon, hence a patient centered approach to care is instrumental. When active disease is present, quarterly monitoring includes intake of patient symptom(s), forced vital capacity (FVC), diffusing capacity of carbon monoxide (DL$_{CO}$), SpO$_2$, 6-minute walk test, chest radiograph (Scadding stages), CBC and CMP. Poor outcome in pulmonary sarcoidosis is largely influenced by interstitial fibrosis and pulmonary hypertension.

FVC and DL$_{CO}$, with ventilatory adjustment (DL$_{CO}$/VA) serve as surrogates. DL$_{CO}$ <60% and FVC <70% portends clinically significant pulmonary sarcoidosis pathology. DL$_{CO}$ reduction to 50% predicted within the first 6 months of disease portends progression of disease and warrants treatment. Walsh *et al*. studied the impact of incorporating a composite physiological index (CPI) taking into consideration vascular issues (DL$_{CO}$), restrictive physiological measures (FVC), and the morphological changes on the HRCT (3). All-cause mortality was chosen

as the primary endpoint for this study of 503 sarcoidosis patients. The CPI and extent of fibrosis were independently predictive of mortality. Moreover, when analyzing the effects on outcome for those treated *vs.* not treated, there was no difference. Both had poor outcomes. Other parameters indicating need for treatment, include patient symptoms in the presence of DL_{CO} between 50–65%, reduction of the FVC and/or chest imaging indicative of disease activity. In Scadding stage 4 pulmonary sarcoidosis, a positron emission tomography (PET) scan and magnetic resonance imaging (MRI) assist to identify active inflammation in the presence of visualized fibrosis and debilitating symptoms. In a retrospective case series of 89 sarcoidosis patients with disabling symptoms, 15 were noted to have stage IV pulmonary sarcoidosis. Fourteen of the 15 patients (93%) had uptake on PET suggesting that inflammation is commonly co-existent with fibrosis (4). FVC and DL_{CO} were lower in the PET positive group compared to PET negative (FVC 91%±26% *vs.* 101%±19%; DL_{CO} 71%±19% *vs.* 80%±15%).

When there is a disproportionate reduction of DL_{CO} <60%, this finding may indicate pulmonary vasculopathy related to cardiac sarcoidosis or associated pulmonary hypertension. A screening echocardiogram is recommended in these situations. The 5-year survival for patients with sarcoidosis associated pulmonary hypertension (SAPH) is 35% (5). Factors associated with increased mortality with SAPH include a reduction in FVC, DL_{CO}, higher pulmonary vascular resistance, a lower cardiac index, pulmonary artery pressure of >50 mmHg and more pulmonary fibrosis. There does appear to be a correlation between DL_{CO} and mean pulmonary artery pressure. The decision to treat sarcoidosis associated pulmonary hypertension needs to be carefully considered as worsening ventilation/perfusion mismatch could ensue, fibrosis could progress, and the patient's functional status with 6-minute walk distance (6MWD) may not improve. Three steps regarding care for patients with SAPH include (I) finding the cause of the pulmonary hypertension; (II) assessing for vascular stenosis; (III) treatment of hypoxia. Treatment of SAPH with Bosentan improves patients' hemodynamics by reducing the mean pulmonary artery pressure by 7 mmHg without changes in 6MWD. It is still unclear whether there is a survival benefit by treating the secondary pulmonary hypertension.

Clinicians should also have a high index of suspicion for cardiac sarcoidosis if there are findings of extra-pulmonary manifestations of sarcoidosis and a disproportionate reduction of DL_{CO} <60%. The history can be quite helpful in guiding the need for further diagnostic testing. The yield with endomyocardial biopsies is <25%. Cardiac imaging provides better diagnostic yield. In cases where the echocardiogram is without concern for cardiac sarcoidosis, then an annual EKG should be assessed. The literature does not clearly differentiate between MRI and PET scanning to assess for the presence of cardiac sarcoidosis, so either can be utilized. Although complete heart block is a worrisome complication of cardiac sarcoidosis, ventricular arrhythmias and congestive heart failure are the two leading causes of sudden death when cardiac sarcoidosis is present. Earlier treatment of cardiac sarcoidosis with steroids and placement of an automated implantable cardiac defibrillator are imperative.

It is estimated that 7–8% of patients have a reduction in life expectancy due to sarcoidosis, primarily in the 20–30% of sarcoidosis patients having lung, cardiac, and nervous system involvement. Questions addressed when deciding whether therapy is warranted include: (I) does the patient exhibit life- or organ-threatening disease? and (II) what is the progression of the disease? Treatment of life threatening consequences includes use of anti-inflammatories, addressing pulmonary fibrosis and pulmonary hypertension, management of infections, and consideration of lung transplant. Optimal response to therapy is not uniform, however. Challenges to optimal outcome include phenotypic variance of the disease and heterogeneity of organ response. While corticosteroids can promote short-term improvements in symptoms and lung function, whether or not they can prevent pulmonary fibrosis is not answered. There was no apparent long-term benefit or harm from the use of systemic steroids (6). In fact many of these patients will need treatment for prolonged periods, sometimes years. When recommending discontinuation of therapy, a step-wise approach over a 9–12 months period has been recommended. Caution should be noted while weaning the corticosteroids. Thirteen to seventy-five percent of patients can show signs of a relapse or acute exacerbation 1 month to 1 year after the taper or discontinuation of therapy (7). Several steroid sparing agents have been studied in conjunction with or as an alternative to corticosteroids. Despite the lack of large randomized double-blinded placebo-controlled trials, these agents are showing beneficial effects depending on the organ involvement. Considerations given to the chosen

therapeutic option are dependent on the tolerability to the medication, the molecular basis, and level of evidence to support its use.

Hydroxychloroquine and pentoxifylline inhibit granuloma formation and antigen presentation, without major suppression of the immune system. Hydroxychloroquine is rather good for hypercalcemia, and cutaneous sarcoidosis, but has limited response in pulmonary sarcoidosis.

Pentoxifylline (1,600–2,000 mg/day) improves DL_{CO} and PaO_2 while modestly reducing the steroid dose (8,9). More recently, Vorselaars *et al*. compared the efficacy between methotrexate (MTX) to azathioprine (AZA) in second line therapy for sarcoidosis (10). This retrospective study included 145 patients receiving methotrexate and 55 who received azathioprine. Both groups showed a reduction in prednisone dose requirement, improvements in the FEV_1, FVC and DL_{CO}. There were more infections noted in the AZA group compared to MTX however (34.6% *vs.* 18.1%, P=0.01). There is also some promise in the use of rituximab in refractory cases of sarcoidosis. In a phase I/II prospective open, labeled study, ten patients with moderate-to-severe pulmonary sarcoidosis with FVC 30–80%, parenchymal involvement on CXR who were persistently symptomatic despite use of corticosteroids plus one or more steroid-sparing agents were provided 1 gm IV rituximab at baseline and 2 weeks (11). The study period was 52 weeks with the primary end-point being safety. The secondary end-points were change in FVC and 6MWD. There was no significant difference in the FVC or chest radiographic stage at 52 weeks compared to baseline. There was however some improvement in the 6MWD.

Acthar gel stimulates the melanocortin receptors (MCRs), which have anti-inflammatory activities. Forty seven patients with multisystem sarcoidosis were identified in a retrospective study (12). They had to have received at least 1 treatment of 80 IU Acthar gel and monitored for at least 6 months. Within 3 months, 18 patients (38%) had to discontinue Acthar due to various issues. The remaining 29 patients (62%) received at least 3 months of therapy. Eleven of these patients (38%) experienced improvement in one or more organs, 16 (55%) remained stable and only 2 (7%) had relapsed after 6 months of therapy.

Pipeline therapies to target pathophysiological areas for sarcoid include Th-17, the Treg pathway, toll-like receptor-2, and the SAA pathway. Therapies for other diseases may also show benefit in sarcoidosis. Atorvastatin inhibits interferon expression on macrophages and LFA-1 dependent stimulation of T cells. Quercetin reduces antioxidant stress and TNF alpha levels. While current therapies for sarcoid seem limited, the future is bright for novel, targeted therapies.

Acknowledgements

Footnote

References

1. Chen ES, Song Z, Willett MH, et al. Serum amyloid A regulates granulomatous inflammation in sarcoidosis through Toll-like receptor-2. Am J Respir Crit Care Med 2010;181:360-73.
2. Chen ES, Moller DR. Sarcoidosis--scientific progress and clinical challenges. Nat Rev Rheumatol 2011;7:457-67.
3. Walsh SL, Wells AU, Sverzellati N, et al. An integrated clinicoradiological staging system for pulmonary sarcoidosis: a case-cohort study. Lancet Respir Med 2014;2:123-30.
4. Mostard RL, Vöö S, van Kroonenburgh MJ, et al. Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis. Respir Med 2011;105:1917-24.
5. Bonham CA, Oldham JM, Gomberg-Maitland M, et al. Prostacyclin and oral vasodilator therapy in sarcoidosis-associated pulmonary hypertension: a retrospective case series. Chest 2015;148:1055-62.
6. Gibson GJ, Prescott RJ, Muers MF, et al. British Thoracic Society Sarcoidosis study: effects of long term corticosteroid treatment. Thorax 1996;51:238-47.
7. Judson MA. An approach to the treatment of pulmonary sarcoidosis with corticosteroids: the six phases of treatment. Chest 1999;115:1158-65.
8. Park MK, Fontana Jr, Babaali H, et al. Steroid-sparing effects of pentoxifylline in pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2009;26:121-31.
9. Zabel P, Entzian P, Dalhoff K, et al. Pentoxifylline in treatment of sarcoidosis. Am J Respir Crit Care Med

1997;155:1665-9.

10. Vorselaars AD, Wuyts WA, Vorselaars VM, et al. Methotrexate vs azathioprine in second-line therapy of sarcoidosis. Chest 2013;144:805-12.

11. Sweiss NJ, Lower EE, Mirsaeidi M, et al. Rituximab in the treatment of refractory pulmonary sarcoidosis. Eur Respir J 2014;43:1525-8.

12. Baughman RP, Barney JB, O'Hare L, et al. A retrospective pilot study examining the use of Acthar gel in sarcoidosis patients. Respir Med 2016;110:66-72.