

## Management Strategies in Sarcoidosis: Why Short-Term Prednisone Monotherapy Is Simply Not Enough

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### Editorial

Despite therapeutic protocols increasingly being composed of multiple agents, it is not all that uncommon for individuals with sarcoidosis to present to sarcoid specialty clinics only on a 2-3 week prednisone course for treatment and not show any resolution of their signs and symptoms. In order to understand why the response is inadequate, we will need to delve deeper into the immunological cascade for this disease process.

A hallmark feature of sarcoidosis is the presence of CD4<sup>+</sup> T cells that interact with antigen-presenting complexes to instigate granuloma formation within tissues [1]. Drent et al. [2] showed that T lymphocytes are predominant in the bronchial alveolar lavage fluid (BALF) obtained from patients with sarcoidosis while B-cells are only present in a small percentage (5%) [2]. Further analysis revealed that sarcoidosis patients had high CD4 to CD8 ratios in the BALF. There is an evolutionary finding that a high CD4/CD8 ratio is not unique to all individuals with sarcoidosis. In fact, patients with sarcoidosis can present with variable CD4/CD8 ratios with correspondingly different symptoms and severity of disease [2]. For instance, non-smoking symptomatic patients with active sarcoidosis have a mean CD4/CD8 ratio of 8.0; versus asymptomatic patients have a CD4/CD8 ratio of 4.7. The principle determinant is from the influx of CD4 T-cells to the alveoli. It is the individuals with the very high CD4/CD8 ratio that have shown spontaneous remission of sarcoidosis. On the other side of the spectrum, individuals with a lower CD4/CD8 ratio (due to influx of CD8 T-cells) develop more chronic disease and pulmonary fibrosis.

It is now being evaluated that the T-regulatory cells (CD4:CD25 bright lymphocytes) are the major contributing factor for the down-regulation of sarcoidosis cell-mediated immune response. Having higher T-regulatory cells present bodes a better prognosis.

### So, why is prednisone alone not sufficient to provide a clinical response in everyone?

In general, prednisone depletes CD4 T-cells in the peripheral blood via lymphocyte re-circulation and modulation of the cellular expression of adhesion molecules [3,4]. Corticosteroids thereby affect the CD4/CD8 ratio of the T lymphocytes located within tissue as well as peripheral blood. They also affect the synthesis and expression of membrane molecules that play a crucial role in lymphocyte function. Hence, with prednisone, there is a proportional increase in circulating CD8 T-cells [5]. Although mice and rat models show that corticosteroids invoke lysis of the lymphocytes, human lymphocytes are somewhat resistant to corticosteroids and relatively refractory to lysis. As noted, this is not an absolute refractory state. There is evidence of transient lymphopenia as a normal response to exposure

to the various therapies, including corticosteroids. In a study where subjects were given oral prednisone, they become depleted in their serum T-cells [6]. Unexpectedly, the proportion of B cells increased after giving steroids. Six hours after ingestion of the steroids, both T- and B-cell levels returned back to baseline levels, indicating a time-dependent response.

It is the migration of epithelial cells and fibroblasts from the interstitium into alveoli and their interaction with the extracellular matrix that are the final common pathway leading to pulmonary fibrosis. Additional investigations have shed light into various contributing factors for the development of fibrosis in sarcoidosis. The activated T- and B-lymphocytes with the proportionally lower ratio of CD4/CD8 do not act alone. 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-2, IL-8), lymphokines, innate (macrophages, neutrophils, eosinophils and mast cells) and humoral immunity (B-cells, antibodies and circulating immune complexes).

Cytokines with pro-inflammatory destructive biological function are locally produced.

TNF- $\alpha$  and IFN- $\gamma$  are both involved in the regulation of sarcoid T-cells [7,8]. They are also involved in promoting local inflammation and granuloma formation. Similar to the CD4/CD8 ratio, some individuals will have higher expression of TNF- $\alpha$  or IFN- $\gamma$  [9]. There are differences between certain heritages having a higher risk for chronic sarcoidosis. For instance, African-Americans demonstrate higher TNF- $\alpha$  levels than patients that are of European-American descent [10]. Unlike the higher TNF- $\alpha$  expression in sarcoidosis leading to pulmonary fibrosis, IFN- $\gamma$  displays a hypersensitivity reaction while inhibiting endothelial cell proliferation and fibroblast collagen synthesis. Once expressed, however, IFN- $\gamma$  induces macrophage production of four important lymphokines (CXCL10, MIG/CXCL9 and ITAC/CXCL11) [11,12]. These lymphokines recruit activated T-cells into the active sites. At local active disease sites, Th1 lymphocytes also release IL-2. IL-2 binds to the IL-2 receptors on fibroblasts enhancing a pro-fibrotic cascade through a coordinated response via monocyte chemoattractant protein (MCP)-1/CC chemokine ligand (CCL) 2. Similar to COPD and cystic fibrosis, higher levels of neutrophils and IL-8/CXCL8 are demonstrated in the airways during active sarcoidosis [13]. Immuno-localization techniques in sarcoidosis have demonstrated that the release of IL-8 is predominantly from pulmonary fibroblasts and less from cellular immunity pathways. The release of this chemokine favors T cell and neutrophil recruitment.

Despite the relative lower amounts of B-lymphocytes noted in the BALF, Fazel et al. [14] found large numbers of B lymphocytes in sarcoidosis pulmonary tissues [14]. These patients are also noted to

have lymphopenia in their blood analysis. This discordance is thought to be due to lymphocyte trafficking from the peripheral blood to the targeted tissue. Sweiss et al. showed that CD4, CD8 and CD19 lymphopenia, measured by peripheral blood, correlated with more severe manifestations of sarcoidosis [15]. While there were patients on medical therapies that have myelosuppression potential, there was no specific finding between lymphocyte count and the medical therapy. It is postulated that the lymphopenia could be related to cytokines suppressing lymphogenesis or an increased apoptosis.

A number of data suggest that the binding of death-signal transmitting receptors or modulators of T-cell apoptosis may have undesirable pathogenic effects in subjects with progressive sarcoidosis. Sarcoid T-cells exhibit resistance to apoptosis, which might contribute to the accumulation of inflammatory cells in the lungs, persistence of inflammation, and the development and maintenance of granulomas [16]. Interestingly, the percentage of T-regulatory cells (Tr), defined as the CD4:CD25 bright lymphocytes is increased in the lungs of patients with active disease who show spontaneous clinical resolution. This suggests that an increased number of Tr in active sarcoidosis may favor the down-regulation of cell-mediated immune response [17].

Challenges to optimal outcome following initiation of recommended therapies include the phenotypic variance of the disease, heterogeneity of organ response, or a lack of uniform response. Treatment recommendations have generally included the start of oral corticosteroids [18]. As indicated above, 2 to 3 week duration of prednisone for treatment is not sufficient course of therapy for resolution of signs and symptoms of sarcoidosis. 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 month period has been recommended. Caution should be noted while weaning the corticosteroids. 13-75% of patients can show signs of a relapse or acute exacerbation 1 month to 1 year after the taper or discontinuation of therapy [19-21].

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. The two medications with the strongest evidence for use include methotrexate and infliximab [22]. I will direct the reader to the reference provided for the mode of actions, dosage and side effect profiles. Other agents used with variable benefits include; azathioprine, leflunomide, adalimumab, cyclophosphamide, pentoxifylline, hydroxychloroquine, and cyclosporine. There is also some promise in the use of rituximab in refractory cases of sarcoidosis [23,24].

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