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Potential Immunotherapies for Sarcoidosis

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Abstract

Introduction: Sarcoidosis is a chronic granulomatous inflammatory disease that commonly causes lung disease, but can affect other vital organs and tissues. The cause of sarcoidosis is unknown, and current therapies are commonly limited by lack of efficacy, adverse side effects, and excessive cost.

Areas covered: The manuscript will provide a review of current concepts relating to the pathogenesis of sarcoidosis, and how these disease mechanisms may be leveraged to develop more effective treatments for sarcoidosis. It provides only a brief summary of currently accepted therapy, while focusing more extensively on potential novel therapies.

Expert Opinion: Current sarcoidosis therapeutic agents primarily target the M1 or pro-inflammatory pathways. Agents that prevent M2 polarization, a regulatory phenotype favoring fibrosis, are attractive treatment alternatives that could potentially prevent fibrosis and associated life threatening complications. Effective treatment of sarcoidosis potentially requires simultaneous modulation both M1/M2 polarization instead of suppressing one pathway over the other to restore immune competent and inactive (M0) macrophages.

Keywords

Sarcoidosis; therapeutic; immunotherapy; macrophage; inflammation; fibrosis; treatment; mechanism

1. Introduction

Sarcoidosis is a rare multisystem granuloma forming disease of unclear etiology. It is likely due to polygenic mechanisms resulting in alteration of the host's immune response to common environmental exposures. Worldwide prevalence ranges from 1 to 40 per 100,000 with adult onset typically before the 4th decade, and disproportionately afflicts African American and Northern Europeans¹. Sarcoidosis can affect almost any organ or tissue, though most commonly affects the lungs, heart, eyes, lymph nodes, and skin. Non-necrotizing granuloma on biopsy supports the diagnosis in the setting of compatible clinical

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Declaration of Interest

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and radiological features². Clinical presentation varies greatly from self-limited or asymptomatic disease to severe phenotypes experience chronic fibrosing disease of one or more vital organs. The highly variable clinical features and diseases course, together with a lack of understanding of disease mechanisms, explains why sarcoidosis treatment is not well standardized. Furthermore, it is clear from recent studies that current treatment options often fail in terms of quality of life indicators such that the disease burden remains unacceptably high^{3,4}. The objective of this article is to briefly review some of the current sarcoidosis treatments, and further emphasizing how disease mechanisms can be leveraged to guide the development of novel therapies.

2. Disease Mechanisms and Goals of Therapy

The immunopathogenesis of sarcoidosis is complex and remains enigmatic. It is postulated that individuals with certain genetic susceptibility develop uncontrolled cell-mediated immune responses when exposed to as yet unidentified antigens. Granuloma formation is presumably initiated by environmental antigens presented by mononuclear cells and is subsequently propagated through recruitment of circulating immune cells to the site of inflammation⁵. In sarcoidosis, undifferentiated macrophages (M0 phenotype) are classically activated (M1 phenotype) via Toll-like receptors located on the cell surface or in the endosome compartment, a transition that requires interferon-gamma (INF- γ). M1 macrophages, in turn, present antigens to T cells via major histocompatibility complex (MHC) molecules and promote further granuloma formation by producing tumor necrosis factor alpha (TNF- α) and IL-12, as well as IL-1, IL-16, and IL-23. TNF- α is critical for granuloma formation through the recruitment of naïve T cells and by promoting pro-inflammatory T helper cell (Th1) polarization. Th1 cells undergo oligoclonal expansion and produce INF- γ to further promote M1 activation. Thus, initial phases of granuloma formation are supported by Th1/M1 immune polarization, which is a state of exaggerated TNF- α and INF- γ ⁶⁻⁸. There is also evidence supporting the role of Th17 cells to support granulomatous inflammation and subsequent fibrosis by secreting IL-17, and a subset of Th17 cells (Th17.1) contribute by producing significant amounts of INF- γ ^{9,10}.

Regulatory T cells (Tregs) are of fundamental importance in sarcoidosis. Self-limited sarcoidosis is characterized by high tissue levels of Tregs, which suppress T cell proliferation and activation by producing anti-inflammatory mediators (IL-10, TGF- β) .. In contrast, patients with chronically active sarcoidosis have fewer Tregs in diseased tissue and paradoxically have higher numbers of peripheral Tregs¹¹. Furthermore, the Tregs of chronically active sarcoidosis patients are functionally less active in terms suppressing pro-inflammatory functions¹².

Mechanisms contributing to a transition from acute inflammation (granulomas) to fibrosis are of particular interest, as tissue fibrosis represents an untreatable manifestation with attendant loss of organ function. As opposed to typical TNF- α and INF- γ mediated M1/Th1 polarization during the acute phase of sarcoidosis, the chronic, fibrotic disease state is associated with polarization towards alternatively activated, immune-suppressive M2 macrophages and CD4 T cells of the Th2 phenotype. The M2/Th2 cytokine profile is proximally regulated by IL-4 and IL-13, which induces STAT6 activation to promote the

production of IL-10 in favor of INF- γ . Lower levels of INF- γ promote fibroblast matrix production leading to tissue remodeling and fibrosis^{13,14}. In milder cases of sarcoidosis the initial pro-inflammatory M1/Th1 polarization phase presumably does not transition to a sustained M2/Th2 phase. Instead, macrophages and T cell populations are restored to an undifferentiated state through the elimination of differentiated/activated macrophages by programmed cell death (apoptosis)¹⁵.

The aforementioned granulomatous response is somehow abnormal in patients with sarcoidosis, persisting in the absence of an identifiable pathogen or foreign body. Chen et al suggest that sarcoidosis is a manifestation of microbial antigens, possibly mycobacterial antigens. Alternatively, an inducible acute-phase reactant and amyloid precursor known serum amyloid A (SAA), was shown to accumulate adjacent to sarcoidosis granulomas and is sensed by TLR2 to induce the release of Th1 cytokines, such as INF- γ and TNF. INF- γ , in turn, inhibits SAA clearance. Chen and colleagues hypothesize that SAA could thereby sustain inflammation in the context of chronic and progressive forms of sarcoidosis¹⁶. Notably, TLR2 is capable of promoting both M1 and M2 immune responses, depending the conditions¹⁷.

Based upon current knowledge, it follows that the goal of immune therapies for sarcoidosis are to achieve a balance between M1/Th1 (inflammation) and M2/Th2 (favoring fibrosis) while maintaining the vigilance of the immune system for the detection of potential pathogens to avoid infections. Emerging concepts in the field of sarcoidosis includes immune modulating therapies to potentially restore M1/Th1 and M2/Th2 balance, whereas antimicrobial agents are proposed by some experts to promote the clearance of chronic infections that are not readily identified by existing laboratory techniques^{15,18}. Figure 1 provides a schematic of putative disease mechanisms, further discussed below.

3. Current Therapies

Sarcoidosis can affect any organ system, with pulmonary involvement in >90% of cases. While as many as 60% of patients experience spontaneous disease resolution; 10 to 30% develop chronic or progressive disease requiring systemic treatment¹⁹. A subset of the latter will not tolerate the available therapies or will progress despite usual therapies to chronic disability with irreversible tissue fibrosis²⁰. We will begin with a discussion of commonly used immune modulating therapies for which the mechanism of action is understood.

3A. Corticosteroids

Corticosteroids (CS) are considered the first line therapeutic approach due to potent and rapid anti-inflammatory actions. CS have diverse mechanisms of action, including the inhibition of TNF- α , INF- γ , and related (e.g., NF- κ B) signaling pathways²¹. However, the optimal treatment dose and duration of therapy are not standardized due to lack of adequately powered randomized-controlled clinical trials. When used in the short term, CS can dramatically improve disease related symptoms, normalize molecular biomarkers, restore lung function, and x-ray findings^{22,23}. However, their long-term effects/benefits are unclear in that they often fail to slow disease progression, prevent fibrosis, and there is no proof that they improve survival. CS have numerous side effects and these contribute to a

decreased perceived quality of life in CS treated patients compared to those with similar disease manifestation who are not treated¹⁵. Despite the unfavorable side-effect profile of CS, they are the mostly widely used first line therapy, especially in acute life threatening or symptomatic disease.

3B. Cytolytic Agents: Nucleotide Analogues and Precursor Analogues

Methotrexate (MTX) is commonly used as a second line therapy for sarcoidosis. MTX targets dihydrofolate reductase, a critical enzyme for folic acid metabolism required for purine and thymidine (DNA) synthesis. However, DNA integrity is not influenced significantly at within the lower dose range (10–20 mg/week) used for the treatment of sarcoidosis¹⁸. Within this dose range MTX induces the extracellular release of adenosine, a potent regulator of M1 and M2 macrophages, favoring polarization towards the latter. As proof of this concept, *in vivo* and animal studies of chronic inflammation showed MTX was ineffective in the presence of adenosine antagonists, adenosine deaminase, adenosine receptor antagonists, or the deletion of adenosine receptors²⁴. MTX suppresses TNF- α production via adenosine A2A receptors while inducing IL-4 and IL-13, upstream regulators of M2 polarization. MTX can also polarize M0 to M2 via IL-4 receptor independent pathways²⁰. Thus, the desirable anti-inflammatory actions of MTX are offset by an increased risk of fibrosis²¹. Other undesirable side effects of MTX, such as hair loss, leukopenia, anemia, relate to the anti-metabolic actions, which are mitigated by folic acid supplementation.

MTX is used clinically either as a “CS-sparing” agent or as the sole agent for patients requiring chronic immune suppression for sarcoidosis^{22,23}. Evidence of clinical efficacy for MTX is extrapolated from a handful of trials, mostly retrospective and conducted in the setting of concomitant CS use, and demonstrating synergy with concomitant use of MTX and CS. MTX is often used in conjunction with other therapies (e.g., anti-TNF- α) to optimize disease suppression, while exploiting its favorable side effect profile.

Azathioprine (AZA) is a purine analog that can block DNA and RNA synthesis thereby suppressing T- and B-cell proliferation. AZA has been shown to inhibit T-cell/APC (antigen presenting cell) engagement and related T-cell activation and IFN- γ production^{25,26}, such as occurs during early granuloma formation. Whereas randomized controlled trials assessing AZA efficacy in sarcoidosis are lacking, an open-label clinical trial of 11 patients with steroid-dependent chronic sarcoidosis demonstrated synergy of AZA with CS in terms of less severe symptoms and improved physiological, serological, and radiographic parameters²⁷. Likewise, a retrospective analysis compared 145 patients compared MTX with AZA showing similar benefits, as reflected by CS-sparing effects and improvement of FEV1 and DLCO. However, AZA treatment was more often complicated by infections²⁸.

3C. TNF-alpha inhibitors

For those who fail to respond to or are unable to tolerate corticosteroids, MTX or AZA, anti-TNF- α agents can be an effective alternative. As shown in Figure 1. TNF- α is crucial for the formation and maintenance of granulomas²⁹. Many of the therapies commonly used for sarcoidosis influence TNF- α production or function.

3C.1 Inhibitors of TNF- α production—Pentoxifylline (POF) is a methylxanthine derivative and a non-selective phosphodiesterase inhibitor. POF modulates inflammation by suppressing cytokine production in macrophages. *In vitro* studies indicate that POF was comparable to CS as an inhibitor of spontaneous and LPS-induced production of TNF- α , IL-6, -8, and -10 by alveolar macrophages.^{30–32} Efficacy of POF was demonstrated in a randomized, double-blind, and placebo-controlled trial of 27 sarcoidosis subjects treated with POF in which fewer sarcoidosis flares and lower corticosteroid dependency were reported³³. Another clinical trial enrolled 23 treatment-naive pulmonary sarcoidosis patients who were treated for 6 months with POF, of which eleven had improved DLCO and PaO₂ after 6 months to follow up, and seven had stable disease³⁴. This was an observational trial lacking a control group, and many patients were excluded at the time of screening. The inconvenient dosing of the POF (thrice daily) and frequent gastrointestinal side effects limit the routine use of this drug for the treatment of sarcoidosis.

Thalidomide is a suppressor of TNF- α production that has been successful in treating granulomatous diseases, such as leprosy and tuberculosis. Thalidomide accelerates TNF- α mRNA degradation, and has been shown to reduce TNF- α production by alveolar macrophages^{35,36}. However, clinical data on thalidomide for sarcoidosis are not promising. A randomized, double-blind, placebo controlled trial evaluating efficacy for the treatment of cutaneous sarcoidosis reported frequent adverse side effects and lack of efficacy³⁷. Likewise, a prospective open-label of 10 patients with corticosteroid-dependent pulmonary sarcoidosis showed no improvement of spirometry, quality of life, or dyspnea after 24 weeks of thalidomide. Moreover, 90% of patients experienced intolerable side effects³⁸. Another small observational study (19 patients) treated for 24 months with low-dose thalidomide showed improved skin, x-ray, and pulmonary function (lung diffusing capacity); however these benefits were offset by the high frequency of adverse events³⁹. Thalidomide is also prohibitively expensive, and other anti- TNF- α treatments are better tolerated, which explains why thalidomide is rarely used for the treatment of sarcoidosis.

Apremilast is a phosphodiesterase-4 inhibitor that is used for psoriasis that potently suppresses TNF- α production⁴⁰. There is very limited data supporting the use of Apremilast for the treatment of sarcoidosis. Encouraging results were reported following the treatment of 18 patients with cutaneous sarcoidosis in whom an objective improvement of skin manifestations was documented⁴¹, but the effect of treatment in other organ systems has not been established. The high cost of Apremilast currently limits the routine use of this drug for sarcoidosis.

3C.2 Biological TNF-alpha blocking agents—Biological agents show great promise for sarcoidosis treatment given their specificity. Infliximab is a murine chimeric monoclonal antibody against the soluble component of TNF- α to prevent its interaction with TNF- α receptors. Infliximab is administered IV over 2–4 hours, requires several loading doses, followed by regular maintenance dosing at 4–8 week intervals. Infliximab is the most studied biological agent for sarcoidosis treatment, mostly focused on patients who are refractory or intolerant of conventional treatments for sarcoidosis^{42–46}. However, infusion reactions or neutralizing antibody formation are common, necessitating the concomitant use of other immune suppressants.

Other anti-TNF- α agents are less well studied. Adalimumab is a human anti-TNF- α monoclonal antibody shown to be effective in refractory cases of sarcoidosis^{47,48}. In a retrospective study of 18 patients unable to tolerate Infliximab who were subsequently treated with Adalimumab, there was a reported clinical improvement in 39%, stabilization in 33%, and 28% had worsened disease⁴⁹. Etanercept, a dimeric fusion protein designed to bind the human TNF receptor extracellular ligand-binding domain, is not shown to be effective for sarcoidosis. For instance, of 17 patients with progressive pulmonary sarcoidosis treated with Etanercept, a majority had treatment failure. Others with chronic ocular sarcoidosis (n=9) had no significant improvement with Etanercept when compared to placebo (n=9)^{50,51}. Moreover, a number of case reports indicate that Etanercept paradoxically triggers a sarcoidosis-like illness⁵². Golimumab, another human monoclonal anti-TNF- α antibody, was carefully studied in a multicenter, randomized, three-arm, double-blind trial compared to placebo and Ustekinumab (a dual IL-12 and IL-23 inhibitor) for the treatment of pulmonary and/or cutaneous sarcoidosis. Unfortunately, neither agent showed significant benefit compared to placebo⁵³.

At present, infliximab and adalimumab are most commonly used for the treatment of refractory forms of sarcoidosis. The high cost of these medications, and the increased risks of infections, and to a lesser degree malignancy and neurological complications, are barriers to their routine use.

4. Novel Therapies

4A. Interferon-gamma pathway inhibitors

The active inflammatory form of sarcoidosis is characterized by an exaggerated production of TNF- α and INF- γ . INF- γ is produced by pro-inflammatory T-cells (Th1), and is maintained through continuous positive feedback loop by M1 macrophages leading to sustained M1/Th1 polarization. As such, INF- γ is a potential therapeutic target in sarcoidosis. By partially blocking INF- γ , there is the potential to depolarize M1 back to an inactive (M0) state. In this state, inflammation could be controlled while the innate immune system retains the capacity to resist infections and malignancies. Though never tested in humans, quinolone derivative TAK-603 was shown to block INF- γ production by BAL cells of sarcoidosis patients, and was touted as a possible treatment for refractory sarcoidosis⁵⁴. Fontolizumab, a humanized monoclonal antibody against INF- γ , has been tested in clinical trials to treat moderate to severe Crohn's disease. Crohn's disease is similar to sarcoidosis in that the disease is presumably provoked by environmental antigenic triggers in genetically predisposed individuals forming non-caseating granulomas, a M1/Th1 INF- γ driven process^{55,56}. However, the results of a single randomized, double-blind, placebo-controlled, and multiple-dose trial of 201 patients with moderate to severe Crohn's Disease receiving anti-INF- γ treatment, was disappointing^{57,58}. Whereas Fontolizumab was safe and well-tolerated, efficacy was lacking. The potential role of this drug as a treatment for sarcoidosis is unclear.

4B. Targeting M2 Polarization

Currently therapeutics primarily target pro-inflammatory pathways⁵⁹. However, M2 polarization in sarcoidosis promotes fibrosis and associated irreversible tissue damage culminating in the most severe disease manifestations. The same is true of asthma and COPD, wherein treatment-refractory cases are associated with airway remodeling and lung fibrosis^{60–62}. Thus, there is increasing interest in therapeutics designed to prevent M2 polarization in chronic inflammatory diseases, including sarcoidosis. As per Figure 1, M2 polarization is proximally regulated by IL-4 and IL-13 to promote the expression and phosphorylation of STAT-6, a transcription factor that promotes a signaling cascade that includes the PPAR- γ pathway⁶³.

Leflunomide, a promising treatment for sarcoidosis, is a tyrosine kinase inhibitor preventing STAT-6 phosphorylation. Leflunomide also regulates inflammation by suppressing Th17 cells and promoting the function of regulatory T cells (Tregs)^{62,64,65}. The largest trial of Leflunomide for the treatment of sarcoidosis was a retrospective analysis of 76 patients with pulmonary and extrapulmonary disease. Leflunomide treatment resulted in significant improvement in lung function, as reflected by forced vital capacity (FVC), and was CS sparing⁶⁶. Additional, prospective studies are needed to validate this encouraging report.

Doxycycline and related drugs (minocycline, tetracycline) inhibit M2 polarization in vitro⁶⁷, and are used clinically for sarcoidosis. The mechanism of action of this drug class is unclear, but may relate to dose-dependent inhibition of STAT6. In a small related study of twelve patients with cutaneous sarcoidosis treated with minocycline, eight had a complete clinical response and two had a partial response. Three patients experienced a relapse, but remission was subsequently achieved when treated with doxycycline⁶⁸.

Dupilumab is a new biological agent that modulates M2/Th2 polarization. It is a fully human monoclonal antibody against interleukin-4 receptor alpha. As such, Dupilumab can inhibit both IL-4 and IL-13 signaling, and has been used in moderate to severe asthma and atopic dermatitis with encouraging results^{69,70}. It is reasonable to postulate that Dupilumab could be useful for the prevention of granulomatous inflammation in the context of active sarcoidosis.

4C. Antibacterial Therapy

Chronic stimulation of APCs and T-cells with immunogenic molecules can promote granuloma formation, and this is postulated to be the case in sarcoidosis. The source of disease-causing antigens is unclear; however, microorganisms such as *Mycobacterium* and *Propionibacterium* are of primary interest⁷¹. Although viable organisms are not present in sarcoidosis (by definition), molecular testing confirms the presence microorganism DNA at a higher rate in patients with sarcoidosis. Furthermore, *Mycobacterium tuberculosis* catalase-peroxidase protein is commonly detected in sarcoidosis patients^{72,73}. Could this finding represent insidious infection? To address this question a randomized, placebo controlled trial of 30 patients with cutaneous sarcoidosis investigated the effects concomitant levofloxacin, ethambutol, azithromycin, and rifampin (CLEAR protocol) treatment for 8 weeks, showing significant improvement in the size of cutaneous sarcoidosis lesions⁷⁴. The

CLEAR protocol also showed benefit in a small cohort (n= 15) with chronic pulmonary sarcoidosis, based on significant improvement of FVC, and quality-of-life metrics⁷⁵. An ongoing NIH-supported multicenter, randomized, double-blind, place-controlled trial is underway to investigate CLEAR for progressive pulmonary sarcoidosis. It is important to note that the antimicrobial components of CLEAR may, like doxycycline, have intrinsic anti-inflammatory effects, such that demonstration of efficacy does not prove a causal link between active infection and sarcoidosis.

4D. Nicotine Therapy

Epidemiological studies suggest that chronic smoking is a protective factor for granulomatous diseases, particularly sarcoidosis^{76–78}. In this regard, nicotine engagement with alpha-7 nicotinic cholinergic receptor ($\alpha 7nAChR$) on macrophages interferes with NF- κB activation and translocation to the nucleus mediated by the JAK-2/STAT3 pathway⁷⁹. As shown in Figure 1, NF- κB is needed for M1 polarization and pro-inflammatory cytokine production. Nicotine's effects on CD4 cells includes a reduction of Th17/Treg ratio⁸⁰. Testing the hypothesis that nicotine may be of benefit in sarcoidosis, a small (n=13) randomized, controlled clinical trial evaluated the effect of nicotine treatment for 12 weeks in conjunction with conventional therapy on surrogate inflammatory endpoints. Compared with conventional therapy alone, transdermal nicotine normalized Toll-like receptors (TLR)-2 and TLR-9 responsiveness and increased the prevalence of specific "pre-activated" Tregs in sarcoidosis patients. Furthermore, no significant tachyphylaxis was observed in this trial as reflected by nicotine receptor expression on circulating immune cells⁸¹. Nicotine is an appealing therapeutic option because it is readily available (FDA approved for other indications) and could be readily repurposed for the treatment of sarcoidosis.

Nicotine has many side effects, some of which may be beneficial for patients with active sarcoidosis. Besides symptoms arising from directly involved organs, patients with sarcoidosis have high prevalence of non-specific quality-of-life-altering symptoms such fatigue, cognitive slowing, depression, and anxiety^{3,4}. Nicotine is shown to improve mood, alleviate depression, and increased self-rated vigor in non-sarcoidosis patients^{82–85}. There is an ongoing NIH/NHLBI-support clinical trial to further investigate nicotine's effects on sarcoidosis treatment which is designed to further evaluate the safety of nicotine and to initially evaluate surrogate biomarkers reflecting pulmonary disease resolution (NCT02265874).

4E. Immunotherapy to Restore Normal Granuloma Function

While most experts believe sarcoidosis to be an exaggerated immune response to common environmental exposures, some posit that sarcoidosis to be an impaired immune response (immune exhaustion) that fails to effectively clear immunogenic antigens. Immune checkpoint inhibitors are a class of molecules that suppress immune responses to antigenic stimulation. Programmed cell death protein 1 (PD-1) and its receptor/ligand (PD-L1) are potent immune checkpoint inhibitors and are molecule of interest for the reversal of immune exhaustion by restoring T cell cytokine responses and proliferation capacity. It has been shown that T cells from patients with active progressive sarcoidosis T cells exhibit increased PD-1 expression and reduced proliferation capacity when compared to self-limited disease

phenotypes, and PD-1 blocking antibodies restore T cell proliferative capacity and function^{86,87}. Likewise, cytotoxic T lymphocyte antigen 4 (CTLA-4) is a molecule expressed on activated T cells which inhibits T-cell activation and proliferation by blocking B7 with CD28 co-stimulation. CTLA-4 blockage increases Th17 while impairing Tregs functions, which has important implications for sarcoidosis pathogenesis^{88,89}. CTLA-4 expression therefore might be a potential therapy to promote more effective antigen clearance.

While anti-PD-1 and anti-CTLA-4 therapy do enjoy success in the realm of cancer, no data is yet available for sarcoidosis. However, there are case reports of patients experiencing a flare of preexisting sarcoidosis, and new onset of sarcoid-like reactions while on anti-PD-1 or anti-CTLA-4 therapy for different diseases process⁹⁰⁻⁹². Such reports highlight uncertainties relating to the pathogenesis of sarcoidosis, and further suggests that optimal treatment of sarcoidosis may involve achieving a balance between the extremes of pro-inflammatory (granuloma promoting) and regulatory (pro-fibrotic) pathways so as to restore normal tissue and immune cell function.

4F. B-Cell Therapy

The role of B cells in the pathogenesis of sarcoidosis is unclear, but emerging evidence suggests that they do play a supporting role. Sarcoidosis patients often have evidence B cell hyperactivity, such as hypergammaglobulinemia, autoantibody production, and circulating immune complexes, such as is typically seen in patients with autoimmune disease⁹³. While B cells are normally not detected within granulomas, they are more abundant in surrounding tissues. In the context of severe chronic sarcoidosis these B cells, like T cells, are functionally altered, exhibiting blunted responses to antigenic stimulation, as reflected by reduced expression of activation markers, decreased proliferation, and impaired cell differentiation⁹⁴. During the early stages of granuloma development it is proposed that M1/Th1 IFN- γ production increases B-cell-activating factor (BAFF), which plays an important role in B-cell maturation and function leading to an exaggerated autoimmune reaction. It has been demonstrated BAFF is elevated in sarcoidosis and may serve as a biomarker of the disease. *In vitro* studies show that IFN- γ increased BAFF production by monocytes, and was associated with enhanced IL-10 and immunoglobulin production. These B cell populations regressed with effective anti-TNF α treatment, suggesting a supportive role in disease pathogenesis^{93,95,96}.

Rituximab, a humanized anti-CD20 monoclonal antibody used to deplete B cells, has been investigated in sarcoidosis patients failing to respond to other therapies. In contrast to anecdotal success reported in a few case reports, a prospective, open-label trial involving 10 patients with treatment refractory pulmonary sarcoidosis showed no clear clinical benefit, and perhaps increased harm (one death)⁹⁷. While this particular disease phenotype may not benefit, other disease phenotypes, such as those with high immunoglobulin titers or with autoimmune features, may respond better. Further investigation is needed to determine if a more personalized approach to treating sarcoidosis will improved clinical outcomes.

5. Conclusions

Sarcoidosis is a rare multisystem granulomatous disease of unclear etiology. The clinical presentation varies greatly from one individual to the next, ranging from asymptomatic or self-limited disease compared with others experiencing chronic progression, tissue fibrosis and life altering disease manifestations. Current mainstays of treatment include corticosteroids, cytolytic agents, and TNF- α targeted therapies. At present, treatment decisions are not tailored to specific disease phenotypes or related disease mechanisms. In this regard, it is apparent that some individuals exhibit active inflammation, conforming more to a Th1/M1 phenotype, whereas others present with progressive fibrosis and loss of organ function, presumably reflecting M2 polarization. We speculate that a “one size fits all” approach to treating sarcoidosis is not ideal, and that some patients may benefit from anti-inflammatory treatments targeting Th1/M1 immune responses, whereas others may benefit from treatments that block regulatory/pro-fibrotic Th2/M2 polarization. Ideally, a balance would be struck to restore the immune system to a “resting state” wherein immune surveillance is intact and granulomatous inflammation is suppressed.

6. Expert Opinion

Sarcoidosis was first described in 1869; however, fundamental concepts relating to its pathogenesis remain unclear and optimal treatment protocols are not well standardized due to the lack of well-designed clinical trials. Sarcoidosis is traditionally thought to be M1/Th1 driven process, and current mainstays of treatment for sarcoidosis primarily target the M1 inflammatory pathways. More recently, M2/Th2 polarization is emerging as a concern as relates to disease resolution in the form of chronic fibrosis with life threatening complications. We posit that the ultimate goal of sarcoidosis treatment is to restore a healthy balance of inflammatory and regulatory pathways, with the goal of “resetting” the immune system such that immune competence remains intact to reduce the risks of infection and malignancy. Treatment of sarcoidosis therefore could potentially benefit from simultaneous modulation and fine tuning of M1/Th1 and M2/Th2 pathways rather than targeting one pathway or the other.

Large knowledge gaps currently exist in the field of sarcoidosis due, in part, to the lack of appropriate models to study disease mechanisms and treatment outcomes. In this regard, and as an example of how models could be of benefit, a mathematical model of the granulomatous immune response during sarcoidosis has been recently developed and was validated compared to human disease⁹⁸. Models such as these could be used to accelerate our understanding of disease mechanisms, to predict clinical responses, and to guide the design of clinical trials involving one or more immunotherapeutic agents while keeping costs down. However, these models do have limitations in that they are built upon existing concepts of disease pathogenesis, for which many unanswered questions remain.

One of the great unknowns of sarcoidosis relates to the early stages of granuloma formation. Experiments performed on isolated cell lines or in human tissues do not represent the complex interactions of diverse immune cells during granuloma-neogenesis. To address this research limitation, we have developed a novel in vitro human granuloma model that is

shown to mimic many of the molecular features of human tissue granulomas⁹⁹. This model will be useful for refining our understanding of mechanisms regulating early granuloma formation, and the model provides a high throughput platform for pre-clinical testing of novel therapies or for more precisely guiding the treatment of individuals with distinct disease phenotypes. Biomarkers associated with early granuloma formation and reflective of distinct disease mechanisms may ultimately serve to guide therapeutic decisions.

As is the case for other rare diseases, international collaboration between sarcoidosis centers will be important to make future advancements. We propose to establish standards of clinical and research practice among a network of “centers of excellence”. Such centers would provide a platform for more rapidly advancing scientific research, including the identification and testing of novel therapeutic targets in well-designed clinical trials. Such centers would reach out to the regional sarcoidosis communities to provide education, access to care, and to research trials. In so doing, future investigations will be inclusive of underserved populations that are often excluded from clinical trials, many of which (e.g., African American women) have the most severe sarcoidosis disease manifestations. In collaboration with the National Institutes of Health, National Heart Lung and Blood Institute, a Workshop on Sarcoidosis was convened in 2015 to “leverage scientific advancements to understand sarcoidosis variability and improve outcomes”^{100,101}. Among the recommendations of the expert panel was to prioritize clinical trials for severe sarcoidosis phenotypes, and to consider novel trial strategies, such as “randomized withdrawal design”¹⁰² in order to address the limitation of conducting conventional randomized, controlled clinical trial in cohorts of limited sizes.

With the recent advent of more advanced research tools, and plans to create more standardized and sophisticated clinical research networks in the near future, the field of sarcoidosis is now poised to establish precision therapies for patients with diverse sarcoidosis disease manifestations.

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Article Highlights

- Sarcoidosis etiology is unclear at this point, but likely due to polygenic mechanisms and maladapted host's immune response to common environmental exposures resulting in highly variable clinical phenotypes.
- Current therapy primarily targets M1/Th1 inflammatory pathway, but M2/Th2 inhibitory agents could potentially be beneficial in preventing fibrosis and lethal complications.
- Sarcoidosis treatment might require restoration of a healthy balance of inflammatory and regulatory pathways by modulating both M1/M2 instead of targeting one over the other.
- Lack of reliable research models for sarcoidosis hinders progress towards elucidating disease mechanisms and establishing novel therapies.
- Collaboration among sarcoidosis centers with commitment to develop highly standardized and reproducible scientific techniques to accelerate scientific discovery and to promote effective clinical trials.

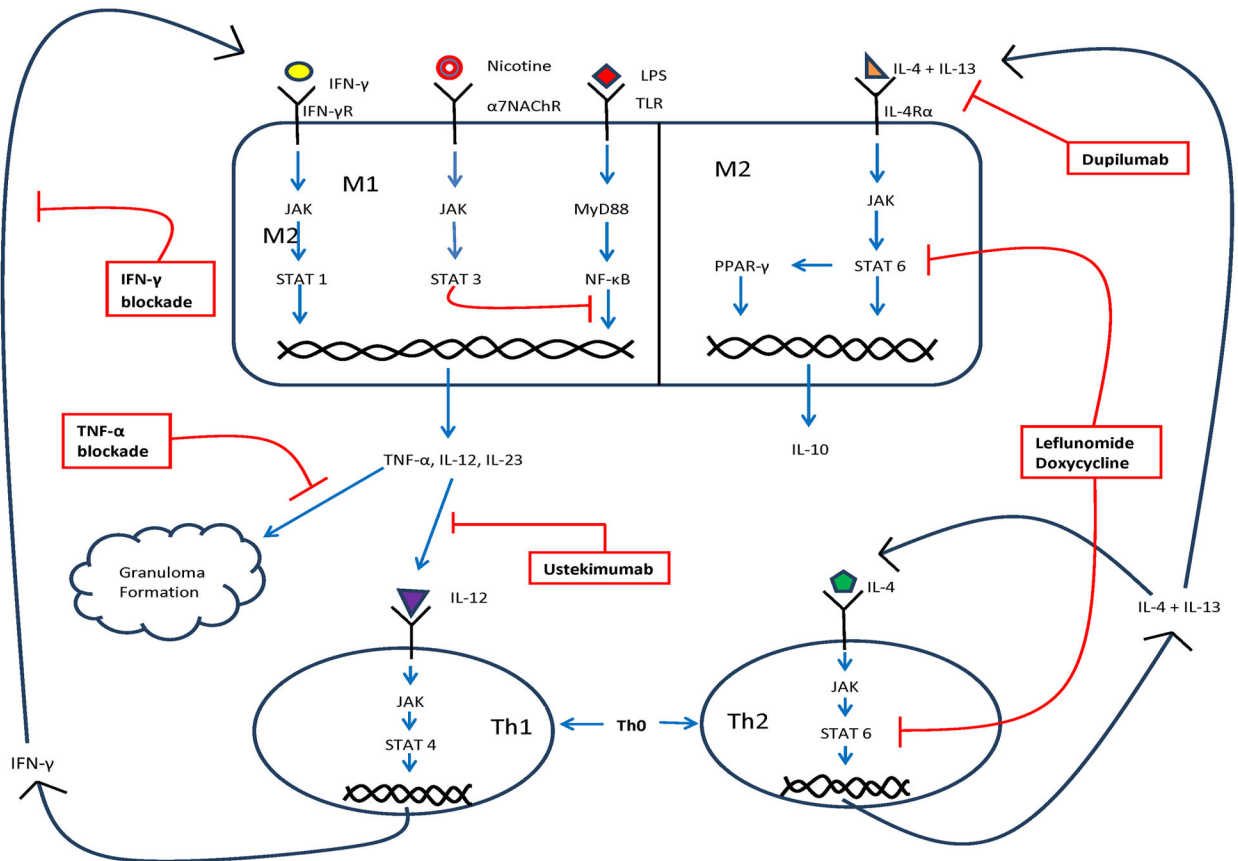


Figure 1. Schematic depicting mechanisms of sarcoidosis granuloma formation and potential therapeutic targets.