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Targeting CD4⁺ T cells for the treatment of sarcoidosis: a promising strategy?

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Abstract

Sarcoidosis is an inflammatory disease of unknown origin characterized by the abnormal accumulation of noncaseating granulomas at sites of disease activity in multiple organs throughout the body with a predilection for the lungs. Because the exact trigger that leads to disease activity is still under investigation, current treatment options are contingent on the organ or organs affected. Corticosteroids are the therapy of choice, but antimalarials and TNF- α antagonists are also commonly prescribed. Recent findings provide evidence for the use of CD20 B-cell-depleting therapy as an alternative method of choice. However, because sarcoidosis is predominantly a T-helper cell-driven disorder, an overwhelming amount of compelling evidence exists for the use of CD4⁺ T-cell targeted therapy.

Keywords

anti-CD20 therapy; corticosteroids; granuloma; sarcoidosis; T helper cells; TNF- α antagonists

Sarcoidosis epidemiology & immunopathogenesis

Sarcoidosis is a multisystemic inflammatory disease of unknown etiology. It is characterized by the abnormal accumulation of noncaseating granulomas in multiple organs throughout the body [1]. Pulmonary involvement is observed in the majority of cases, but a high incidence of lymph node, eye and skin involvement have also been well documented [2]. Two-thirds of individuals will develop an acute form and spontaneously resolve the disease. Some may even develop an asymptomatic form of the illness in which the granulomas will generally disappear without therapeutic intervention [3]. The remaining one-third, however, will acquire a chronic form of the disease that will progress, resulting in severe loss of function or permanent organ damage [4]. The disease will result fatal in about 10% of these

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patients [3]. Older patients are more susceptible to the chronic form of the disease and therefore have a higher mortality rate. Although sarcoidosis can affect anyone, in the USA it is most commonly diagnosed in females of African–American descent between 20–50 years of age [2,5]. Because there is yet to be produced a definitive test for sarcoidosis, the diagnostic approach is one of exclusion based on the presence of noncaseating granulomas, the involvement of multiple organs, as well as the elimination of other granuloma-causing illnesses [6–8].

A suggested model for granuloma formation was recently published in which macrophages, dendritic cells and lymphocytes, with the aid of cytokines and chemokines, collaborate with one another. It is proposed that the process is initiated by an unknown antigen binding to a toll-like receptor. This antigen is then delivered by interstitial dendritic cells to the mediastinal lymph nodes; thereby, commencing the differentiation and clonal expansion of T helper 1 and 17 (Th1/Th17) cells. Alveolar macrophages simultaneously produce tumor necrosis factor- α (TNF- α) resulting in the upregulation of adhesion and activation molecules such as HLA-DR, CD80/86, and ICAM-1, among others. TNF- α , in conjunction with interferon- γ (IFN- γ) produced by natural-killer (NK) cells, stimulate macrophages to make chemokine ligands that attract Th1/17 cells, monocytes, regulatory T cells (Tregs) and B cells. The persistent stimulation from antigen-presenting cells coupled with the presence of Th1/17 favoring cytokines in the lungs results in the incessant recruitment of cells to the inflammatory site, ultimately leading to the formation of granulomas [9] (Figure 1).

It has long been accepted that sarcoidosis is predominantly a T-helper (Th) cell-mediated disease. In 1981 Hunninghake and Crystal sought to investigate the proportion of Th cells to suppressor T cells (Tregs) at sites of disease activity. They observed a significant 10.5:1 ratio of Th cells to Tregs at sites of high-intensity alveolitis in the sarcoidosis patients. This was in contrast to their findings in both control subjects and patients with idiopathic pulmonary fibrosis (IPF), a nongranuloma-forming chronic lung disease. The ratio of Th cells to Tregs in these patients was approximately 1.8:1 [10]. Furthermore, in 1983 Pinkston *et al.* detected spontaneous IL-2 production by pulmonary T cells at sites of disease activity, indicative of Th immunologic response [11].

The exact trigger that leads to the development of sarcoidosis is still under investigation. However, environmental factors, genetics and bacterial antigens are felt to play a critical role in disease development [12,13]. Genetic research has shown a correlation between MHC class II genes and disease susceptibility, as well as, resistance [13,14]. A Case–Control Etiologic Study of sarcoidosis [7] performed high-resolution typing for the HLA class II loci and statistically compared information submitted from biopsy-confirmed cases from ten centers within the USA. The 474 ACCESS patients were matched for age, race, sex and geographic area with 706 control subjects. There were three alleles identified as risk factors for sarcoidosis: HLA-DRB1*1101, 1501 and 1201. Four were recognized as protective: HLA-DRB1*0401, 0404, 0407 and 1503. Interestingly, HLA-DRB1*1101 resulted at a higher incidence in females than in males. Additionally, it was flagged as a risk factor for both African–Americans and Caucasians. There were two other allele risk factors for African–Americans: HLA-DRB1*1201 and HLA-DPB1*0101, and for Caucasians: HLA-DRB1*0402 and HLA-DRB1*1501. HLA-DRB1*1503 and HLA-DRB1*0401 were

identified as being protective in African-Americans and Caucasians, respectively. The HLA-DRB3 allele showed up as a significant risk factor for African-Americans, but not Caucasians. The DRB4 locus, on the other hand, was correlated with having a protective effect in African-Americans but not Caucasians [14]. The strong association of MHC class II alleles with sarcoidosis pathogenesis further supports the importance of CD4⁺ T cells in its pathogenesis.

Current treatments for sarcoidosis

Table 1 summarizes the type of therapy used to treat specific forms of sarcoidosis, their mechanisms of action and complications/toxicities that can arise during and after treatment. Treatment is dependent on the organ or organs affected and can vary. Those diagnosed, but asymptomatic, are rarely treated with pharmaceuticals; the exception being ocular sarcoidosis, in particular sarcoid uveitis, which can result in permanent loss of vision [15]. Critics argue that the lack of treatment in this scenario can result in irreversible fibrosis formation and scarring in the affected organs. However, clinicians agree that these patients have an excellent prognosis and the risks involved in treating such patients with traditional medications do not outweigh the benefits of treatment [15]. These individuals will frequently show an acute form of the disease and will spontaneously resolve it [4]. However, those moderately or severely affected by sarcoidosis are treated with therapeutic agents. Major complications that can arise for these individuals include, but are not limited to, respiratory failure, cardiac and/or hepatic disease [16,17].

Patients with a progressive form of sarcoidosis are generally treated with corticosteroids [15]. Corticosteroids are anti-inflammatory agents that regulate gene activity [15]. Their main mechanism of action occurs via repression of inflammatory genes such as IL-2, IFN- γ and TNF- α —cytokines involved in sarcoidosis granuloma formation. The process begins with a corticosteroid molecule binding to its appropriate receptor on the surface of a cell. This complex is then internalized and transported to the cell's nucleus where it forms a homodimer with other activated receptors. These then bind to DNA sequences termed glucocorticoid response elements (GREs), thereby recruiting co-repressors that aid in the deacetylation of histone proteins. This in turn leads to a condensed chromatin structure that prevent transcription factors from accessing their binding sites, resulting in the obstruction of gene transcription [18,19]. This form of therapy is used to treat several types of sarcoidosis including uveitis, pulmonary, cardiovascular, neurological, cutaneous and granulomatous hepatitis. The effects of corticosteroid therapy on T cells have been well documented. A 1987 study comparing corticosteroid-treated and nontreated patients with active sarcoidosis reported seeing a decrease in IL-2 expression, T-cell proliferation and Th:Treg cells ratio after treatment. Prior to corticosteroid therapy, pulmonary lymphocytes were spontaneously secreting IL-2 at 14.8 U/10 [6] cells. After administration of treatment, IL-2 levels dropped to 0 U/10 [6] cells. Furthermore, preceding therapy, patient T-cell proliferation was 6.7%; whereas, afterwards it significantly reduced to <1% [20]. Because sarcoidosis has been shown to be a predominantly Th cell-mediated disease, Pinkston *et al.* also studied the ratio of Th cells:Tregs [10,11,20]. Before treatment they observed a ratio of 6.8. However, once therapy was given, these same patients showed a decrease to 2.6 with an overall reduction in lymphocyte percentages from 48 to 35%. Additionally, their results

suggested that corticosteroids suppress IL-2 transcription [20]. The use of corticosteroid therapy, however, has been shown to have serious adverse toxic reactions. Additionally, it has been suggested that a correlation exists between the frequency of patient disease relapse and the use of corticosteroid therapy [21–24]. One study reported a 74% relapse rate amongst sarcoidosis patients following corticosteroid withdrawal. Even more interesting was that relapses occasionally occurred in organs that were not initially involved. Furthermore, the frequency at which these patients relapsed was regardless of race. Relapse occurred 2 to 6 months after treatment cessation in 50% of the patients. 20% of the patients went into remission more than 12 months later [21]. These findings mirror those described by another study in which relapse was observed in 75% out of 181 sarcoidosis patients after the removal of low-dose corticosteroid therapy [24].

Nonsteroidal anti-inflammatory agents are prescribed when serious side effects are developed from the use of corticosteroids or when patients require long-term sarcoidosis medication. As aforementioned, CD4⁺ Th cells are found in abundance at sites of disease activity [10,11,25]. It is for this reason that antimalarial therapy is also used to treat sarcoidosis, specifically dermatological, or sarcoidosis with joint involvement and/or hypercalcemia complications [15,26]. These pharmacotherapeutic agents impede antigen presentation to CD4⁺ Th cells. Antimalarials are lysosomotropic agents. These accumulate in acidic cytoplasmic vesicles within antigen-presenting cells (APCs), and as a result, increase their pH. This leads to the inhibition of proteolysis within the vesicles due to interference with the acidic proteases' optimum pH. In order for APCs to present epitopes on their MHC class II molecules to CD4⁺ helper T cells, the antigen must first be ingested by the APC and then be digested within the lysosomal compartment. Additionally, antimalarials inhibit cytokine production; specifically those involved in granuloma formation, such as TNF- α and IFN- γ [15,27]. A serious complication associated with this type of treatment is retinopathy [15,28–32].

Other anti-inflammatory methods of therapy include TNF- α antagonists. This method of treatment acts by neutralizing TNF- α cytokine activity. The pharmaceutical agents contain extracellular domains that bind TNF- α . Once these two molecules are attached, the pro-inflammatory cytokine is prevented from binding to its corresponding two receptors, TNFR1 and TNFR2, thereby blocking its activity [33,34]. TNF- α , as previously stated, participates in the formation of granulomas (Figure 1). Using immunohistochemistry techniques, Fehrenbach *et al.* provided evidence that alveolar macrophages were the main source of TNF- α production at sites of disease activity in pulmonary sarcoidosis. They observed that the highest levels of TNF- α were localized in the areas of alveolar macrophage aggregates [35]. Therefore, the logic behind using this form of treatment is to hinder the development of granulomas. Several cases have been reported documenting the effectiveness of using TNF- α antagonists to treat neurosarcoidosis [36,37]. This type of therapy has also been efficient in treating dermatologic sarcoidosis. One study in particular compared the success rate of using anti-TNF- α pharmaceuticals to other therapeutics on 54 patients with lupus pernio, a disfiguring type of skin sarcoidosis. 33% of patients demonstrated complete resolution, 7% showed near resolution and 32% showed improvement. When compared with other treatment regimens, including corticosteroids, anti-TNF- α therapy resulted in the highest percentage of resolution and near resolution [38].

A 2010 study conducted by Sweiss *et al.* assessed CD4, CD8 and CD19 lymphocyte counts in 28 sarcoidosis patients. Lymphocyte subsets in the peripheral blood of these subjects were significantly reduced, regardless of medication intake. Their findings suggested that the decreased levels of lymphocytes present in the blood of these patients strongly correlated with disease severity [39]. Although, the exact mechanisms responsible for the lymphopenia observed in the peripheral blood of patients with sarcoidosis have yet to be described, one of the contributing factors could include CD4⁺ T cell sequestration at sites of disease activity [40]. TNF- α therapy has been shown to be an effective method of treatment against lymphopenia in sarcoidosis patients [41]. Crouser *et al.* reported improvements in peripheral blood total lymphocyte counts after anti-TNF therapy, as well as, an increase in overall peripheral blood CD4⁺ T cell counts [41].

Despite its efficacy, the drug's high cost and method of administration, intravenously, prevent it from being the first method of treatment [15]. Furthermore, the agent has been associated with increased risk of developing or reactivation of tuberculosis (TB) [42,43]. It was reported that the use of TNF- α inhibitors increased the occurrence of TB in patients with RA from 6.2 to 52.5 patients out of 100,000 [44]. A clinical investigation highlighted the possible mechanisms by which anti-TNF immunotherapy promotes the progression of TB. TNF-blockade treatment reduced perforin and granulysin expression, two antimicrobial effector molecules, in T cells. The same study reported a 29% decrease in CD8⁺ T_{EMRA} cells specific for *Mycobacterium tuberculosis* in patients during therapy [45]. TNF- α antagonists have also been implicated in increasing the threat of other serious infections, such as pneumonia [46]. A 52-week follow-up of a 24-week study in which chronic pulmonary sarcoidosis patients were either given an anti-TNF- α pharmacotherapy agent or a placebo resulted in four out of 91 subjects (4.4%) developing pneumonia after treatment [47]. Another investigation reported that the condition of 86% of sarcoidosis patients worsened soon after the removal of TNF- α antagonist therapy. Within the first 3 months, half of the subjects' condition exacerbated to the point where treatment had to be re-administered [48].

New discoveries & potential treatments

Although considered primarily a T-cell driven disorder, various investigations have reported findings suggestive of humoral mechanism involvement in sarcoidosis such as immunoglobulins, circulating immune complexes and complement [49–52]. Recent histological studies have discovered B-cell localization in the periphery of tissues of sarcoidosis patients [51,53,54]. Furthermore, increased naive and transitional systemic B cells in patients with active sarcoidosis have been observed compared with patients with inactive disease and healthy controls. The patients with active disease also demonstrated decreased memory systemic B cells compared with the control groups. It is also notable that these same patients showed increased levels of IL-10 producing systemic B cells, as well as regulatory B cells involved in downregulating inflammation. Additionally, high levels of B-cell activating factor (BAFF), a phenotype typically associated with auto-immune diseases, was found in the serum of patients with active chronic sarcoidosis [51,54,55]. Not only is BAFF important for providing survival and maturation signals for B cells, but it has recently been shown to also participate in T-cell costimulation [56].

While there is growing evidence for the presence of B cells in sarcoidosis tissues, there is also evidence of reduced functional capacity. Impaired responses in CD19⁺ cells from sarcoidosis patients was demonstrated after stimulating the cells for 24 h and then analyzing their ability to express specific activation markers. Reduced expression of CD25, CD69 and CD86 was observed compared with healthy control B cells. Decreased proliferation after stimulation with CD40L, CpG-ODN, IL-2, IL-10 and IL-15 was seen with levels of $69.3 \pm 11.8\%$ in healthy controls versus $47.9 \pm 16.3\%$ in sarcoidosis B cells. Lee *et al.* also found decreased expression of the costimulatory receptors CD19, CD20, CD21 and CD4, in addition to elevated expression of the coinhibitory receptors CD22, CD32, CD35, CD85J and CD152 by sarcoidosis systemic B cells compared with control cells. The sarcoidosis patients also exhibited a 65% reduction in the levels of NF- κ B in peripheral systemic B cells [55].

CD20 is a calcium ion channel expressed on the surface of B cells, with the exclusion of plasma cells [55,57]. CD20 B-cell depleting therapy employs different modes of action including complement-mediated cytotoxicity, antibody-dependent cell lysis, and the induction of B-cell apoptosis [58]. Anti-CD20 therapy has proven to be an effective method of treatment in autoimmune and inflammatory diseases such as rheumatoid arthritis and multiple sclerosis with limited adverse effects [59,60]. Additionally, cases have been documented showing an improvement with anti-CD20 antibody treatment in sarcoidosis patients, whom have not benefited from using other methods of treatment such as corticosteroid therapy [60–63]. Using acridine orange staining, Mathas *et al.* reported that after 24 h incubation of BL60-2 human Burkitt's lymphoma cells with anti-CD20 antibody 70% of the cells had fragmented nuclei, characteristic of a cell undergoing cell death. This was accompanied by an 80% inhibition of proliferative capacity compared with controls. Furthermore, after only 2 h of stimulation, the cells showed an upregulation of Bcl-2-associated X (BAX) protein. BAX binds to B-cell lymphoma 2 [64] protein, thereby inhibiting its anti-apoptotic ability. The activation of caspase 3 along with its cleavage products SP1 and PARP in the presence of anti-CD20 antibody were also detected [64]. Despite its well-documented success and no apparent severe toxicities, some patients are unresponsive and resistant to B-cell-depleting treatment [65].

Future perspective: CD4⁺ T-cell targeted therapy

Immunosuppressives are used to treat sarcoidosis due to various investigations, such as the ones aforementioned, demonstrating spontaneous release of IL-2 and IFN- γ by T lymphocytes, as well as, monocyte chemotactic factor and other cytokines implicated in granuloma formation at sites of active disease [11,66–68]. Furthermore, it has been reported that sarcoidosis pulmonary T cells show evidence of recent antigen-driven (T-cell receptor) TCR triggering [69]. Recent studies have provided compelling evidence towards antigens from pathogenic mycobacteria or *Propionibacterium acnes* in sarcoidosis pathogenesis [70–73]. A 2005 study identified the presence of *Mycobacterium tuberculosis* catalase-peroxidase (mKatG) in 55% of sarcoidosis tissue samples; whereas, the peptide was not found in any of the control tissues [74]. Mycobacterial heat shock proteins were revealed in sarcoid sera, lymph nodes and circulating immune complexes [75]. This indicates previous exposure to a mycobacterial antigen. A follow-up to the 2005 study, in 2008 Chen *et al.*

tested systemic and localized (bronchoalveolar lavage [BAL]) T-cell antigen responses to mKatG in sarcoidosis patients from two separate cohorts: Sweden and the USA. Despite genetic, demographic and prognostic differences between the subjects, a similar significantly higher percentage of circulating T cells recovered from patients with active disease expressed a positive reaction to the antigen in both cohorts. This was in contrast to healthy volunteers with a negative PPD (PPD-) test. Additionally, an even higher frequency of bronchoalveolar lavage (BAL) T cells from these same patients also derived from sites of active disease reacted positively to mKatG. Interestingly, a greater percentage of mKatG reactive CD4⁺ Th1 cells were localized in the lungs rather than blood, indicating a compartmentalized response. Furthermore, both peripheral blood mononuclear cells (PBMCs) and BAL cells from the same sarcoidosis patients expressed IFN- γ at higher percentages than the control cells in response to mKatG. Molecular analysis of sarcoidosis granulomas reveals mycobacterial DNA in ~80% of specimens, but are absent from granulomatous controls [76,77]. These sequences were most consistent with *M. tuberculosis* (MTB) complex, yet were genetically distinct, suggesting that a novel mycobacterium contributes to sarcoidosis pathogenesis. While confirming earlier observations of an elevated Th1 immune response [20,66,67], it has also been demonstrated that several mycobacterial virulence factors, such as ESAT-6, superoxide dismutase A, Antigen 85A and catalase-peroxidase [78], are immune targets in sarcoidosis CD4⁺ T-cell responses [78–82]. Using an antibody that recognizes lipoteichoic acid specific for *P. acnes*, another study reported positive responses in 88% of fixed granuloma lymph node tissue sections and 57% in fixed lung samples from patients with sarcoidosis, whereas none of the non-sarcoid granuloma tissues from tuberculosis samples reacted positively. These findings suggest a possible link between sarcoidosis and *P. acnes* [72]. A recent investigation assessed the presence of antigen-specific responses to both mycobacterial early secreted antigen target protein [78] and *P. acnes* in CD4⁺ BAL T cells extracted from 27 sarcoidosis patients. The cells were stimulated with either ESAT-6 or *P. acnes* supernatants and then analyzed for intracellular IFN- γ production. 17 of the subjects demonstrated a significantly higher positive response to ESAT-6 than the nontuberculous mycobacteria (NTM) or negative PPD controls. However, the same cells did not show a statistically significant response to *P. acnes* that differed from those seen in control cells. Extracellular cytokine expression of these cells was also analyzed. The ESAT-6 stimulated BAL cells resulted in a higher level of extracellular IL-2 and IFN- γ expression than did *P. acnes*. Moreover, the extracellular cytokine levels secreted in response to *P. acnes* were similar to those seen in the NTM and PPD controls. Even more noteworthy was that the cells that positively responded to both ESAT-6 and *P. acnes* also showed increased proliferation compared with the control cells [70]. These observations supported a trial of antimycobacterial therapy. A blinded, randomized, placebo-controlled analysis of concomitant levaquin, ethambutol, azithromycin and rifampin (CLEAR) therapy was conducted among chronic cutaneous sarcoidosis subjects, as well as an open-label investigation of CLEAR therapy on chronic pulmonary sarcoidosis subjects. In both Phase I trials, significant clinical improvement was observed, and accompanied by normalized expression of p56Lck and CD4⁺ T-cell function, which was absent from subjects who did not improve [83,84].

Intriguingly, a current investigation determined that both sarcoidosis peripheral and bronchoalveolar (BAL) CD4⁺ T cells show spontaneous release of IL-2 and IFN- γ ; however after TCR stimulation, these same cells display an anergic response. Upon TCR stimulation, the CD4⁺ T cells reveal decreased IL-2 and IFN- γ production. Additionally, they display a reduction in proliferative capacity upon TCR stimulation. Tregs also appear to be dysfunctional. Although Tregs were present at higher percentages in sarcoidosis patients, they were unable to suppress CD4⁺ T-cell proliferative ability in both sarcoidosis patients and healthy controls. The observation of reduced function of CD4⁺ Th cells and T-regulatory cells demonstrated global loss of T-cell function. Even more noteworthy is that this is a phenomenon that is reversed upon disease clinical resolution, yet remained present with disease progression [68].

In summary, the observation of increased CD4⁺ T-cell activation supports the application of immunosuppressant medications to minimize localized organ damage and organ compromise, provide patient comfort and improve quality of life. While in most cases, treatment with these agents has proven to be effective in the short term, the side-effect profile remains unacceptable. Immunosuppressant therapy does not irreversibly relieve sarcoidosis pathogenesis and, thus, the impetus to identify alternative strategies remains strong. The observation of restoration of CD4⁺ T-cell capacity in sarcoidosis subjects with spontaneous clinical resolution strongly suggest that a focus on restoration of the immune system is a laudable goal. The application of antimycobacterial therapy as a mechanism for CD4⁺ T-cell immune restoration is preliminary and innovative, warranting further investigation.

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Executive summary

Sarcoidosis epidemiology & immunopathogenesis

- Sarcoidosis is an inflammatory disease of unknown etiology.
- Pulmonary involvement is observed in over 90% of cases.
- Sarcoidosis is characterized by noncaseating granulomas at sites of disease activity.
- Two-thirds of patients will develop an acute form.
- Some patients develop an asymptomatic form in which the granulomas will generally disappear without therapeutic intervention.
- One-third will acquire chronic form of disease that will progress, resulting in severe loss of function or permanent organ damage.
- Sarcoidosis is predominantly a T-helper cell-mediated disease.
- HLA-DRB1*1101, 1501 and 1201 alleles identified as risk factors.
- HLA-DRB1*0401, 0404, 0407, and 1503 identified as protective.

Current treatments for sarcoidosis

- Corticosteroid therapy is treatment of choice for patients with progressive sarcoidosis.
- Nonsteroidal agents such as antimalarials and anti-TNF- α blockers are also used to treat sarcoidosis.
- Current treatment methods have serious adverse affects and risk of relapse.

New discoveries & potential treatments

- Recent histological studies have discovered B-cell localization in the periphery of tissues of saroidosis patients.
- Increased naive and transitional systemic B cells in patients with active sarcoidosis.
- Limited number of cases have been documented showing an improvement with anti-CD20 antibody treatment in sarcoidosis patients.

Future perspective: CD4⁺ T-cell targeted therapy

- Upon TCR stimulation, peripheral and BAL CD4⁺ T cells reveal decreased IL-2 and IFN- γ production.
- Tregs present at higher percentages in sarcoidosis patients, but are unable to suppress CD4⁺ T cell proliferative capacity in both sarcoidosis patients and healthy controls.
- CD4⁺ T-cell global dysfunction reversed upon clinical resolution.

- While in most cases, treatment with immunosuppressives is effective in the short term, patients demonstrate serious adverse effects.
- Immunosuppressant therapy does not irreversibly relieve sarcoidosis pathogenesis.
- Restoration of CD4⁺ T-cell dysfunction as a treatment focus is supported by observation that sarcoidosis subjects with spontaneous clinical resolution demonstrate CD4⁺ T-cell effector function recovery.
- Antimycobacterial therapy as a mechanism for CD4⁺ T-cell immune restoration is preliminary and innovative, warranting further investigation.

Figure 1. Inflammatory response of sarcoidosis with formation of granuloma and subsequent resolution or persistence of disease

Ag: Antigen; HLA: Human leukocyte antigen; IFN: Interferon; IL: Interleukin; TCR: T-cell receptor; TNF: Tumor necrosis factor.

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Table 1

Pharmaceutical agents currently used to treat sarcoidosis.

Drug	Type of sarcoidosis	Mechanism of action	Complications/toxicity
Corticosteroids	NA	Inhibit transcription of specific cytokine genes involved in granuloma development	Varies depending on drug
Prednisone	Acute pulmonary, ocular, lupus pernio, hepatic, joint, cardiac, neurologic, hypercalcemia	Same as above	Relapse, diabetes, osteoporosis
Antimalarials	NA	Lysosomotropic molecules that accumulate in intracellular lysosomes and increase their pH, impeding antigen presentation to CD4 ⁺ Th cells	Varies depending on drug
Chloroquine	Chronic pulmonary, cutaneous, joint, hypercalcemia, joint	Same as above	Retinopathy
Hydroxychloroquine	Neurosarcoidosis, cutaneous, hypercalcemia, joint	Same as above	Retinopathy
TNF-α antagonists	NA	Bind to and neutralize TNF- α activity	
Infliximab	Chronic pulmonary, lupus pernio, uveitis, neurosarcoidosis, cardiac	Same as above	Relapse, tuberculosis, non-tuberculosis infections, allergic reaction, carcinogenic, hepatotoxic, teratogenic
Nonsteroidal anti-inflammatory	NA	Varies depending on drug	Varies depending on drug
Methotrexate	Pulmonary, neurosarcoidosis, cardiac, cutaneous	Inhibits metabolism of folic acid	Hematologic, hepatotoxic, gastrointestinal
Azathioprine	Pulmonary, neurosarcoidosis	Impedes cell proliferation	Hematologic, hepatotoxic, gastrointestinal, teratogenic
Cyclophosphamide	Severe neurosarcoidosis, severe cardiac	Prevents cell division by interfering with DNA synthesis	Sterility, carcinogenic, hematologic, dermatologic, gastrointestinal, genitourinary, teratogenic