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Nonsteroidal therapy of sarcoidosis

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Abstract

Purpose of review—None of the medications used in clinical practice to treat sarcoidosis have been approved by the regulatory authorities. Understanding how to use disease-modifying antisarcoid drugs, however, is essential for physicians treating patients with sarcoidosis. This review summarizes the recent studies of medications used for sarcoidosis with a focus on nonsteroidal therapies. Studies from 2006 to 2013 were considered for review to update clinicians on the most relevant literature published over the last few years.

Recent findings—Several recently published pieces of evidence have helped expand our ability to more appropriately sequence second-line and third-line therapies for sarcoidosis. For instance, methotrexate and azathioprine may be useful and well tolerated medications as second-line treatment. Mycophenolate mofetil might have a role in neurosarcoidosis. TNF-α blockers and other biologics seem to be well tolerated medications for the most severely affected patients.

Summary—Corticosteroids remain the first-line therapy for sarcoidosis as many patients never require treatment or only necessitate a short treatment duration. Second-line and third-line therapies described in this article should be used in patients with progressive or refractory disease or when life-threatening complications are evident at the time of presentation.

Keywords

corticosteroids; disease-modifying antisarcoid drugs; sarcoidosis; TNF-α inhibitor

INTRODUCTION

Sarcoidosis is a granulomatous disease with incompletely understood pathophysiology. It commonly affects the lung, but can involve any organ system. Its presentation ranges from having pulmonary symptoms to nonpulmonary symptoms with variable severity. Given its

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potential to affect multiple organ systems, sarcoidosis is challenging to treat, with therapeutic decisions depending on the organs involved. Furthermore, the U.S. Food and Drug Administration (FDA) has not approved pharmacologic treatments for sarcoidosis, resulting in a lack of standardized management strategies for this disease. Despite the absence of approved sarcoidosis therapies, corticosteroids have become the cornerstone of most therapeutic approaches [1■]. However, the well established side-effects associated with prolonged corticosteroid use make these agents undesirable for chronic disease management. Although typically reserved for the second-line and later settings, nonsteroidal drugs, or what we refer to as disease-modifying antisarcoid drugs (DMASDs), offer an alternative strategy for patients with chronic or complicated sarcoidosis. This article reviews the use of DMASDs in pulmonary and extrapulmonary sarcoidosis.

METHODS: SELECTION OF STUDIES

A literature search was performed for articles published between 2006 and 2013 using the search terms ‘sarcoidosis’ and ‘methotrexate’, ‘TNF-alpha’, ‘mycophenolate’, ‘leflunomide’, ‘azathioprine’, ‘antioxidants’, ‘small fiber neuropathy’, and ‘fatigue’. PubMed, Cinahl, Embase, and the Cochrane Library were searched. Titles of interest were further reviewed by abstract. Reference lists of relevant studies were hand-searched for additional studies. Studies included in this review met the following criteria: study objectives were to describe the effect of the respective medication on clinical symptoms and inflammatory markers in sarcoidosis; study populations included patients with sarcoidosis; articles were full reports, case reports, or reviews; articles were in English; and articles were published in peer-reviewed journals.

PULMONARY SARCOIDOSIS

The decision to treat patients with pulmonary sarcoidosis depends on their pulmonary symptoms, particularly dyspnea and progression of sarcoid parenchymal lung disease. The copresence of extrapulmonary manifestations of the disease, such as hypercalcemia and ocular, cardiac, and neurologic dysfunction, is another consideration for therapeutic intervention [2■]. Once a clinical decision is made to treat a patient, choosing therapy is the next logical determination.

First-line therapy: corticosteroids

In general, corticosteroids are considered the firstline therapy for acute and chronic pulmonary sarcoidosis. Although corticosteroids are the initial drug of choice for almost all forms of sarcoidosis, alternative agents, such as DMASDs, are commonly used. The decision to use these agents is affected by the duration of previous corticosteroid use, the maintenance corticosteroid dose used to control the disease, and the propensity for fibrosis [3]. Several agents have been introduced as DMASDs and are summarized below.

Second-line therapy

Antimetabolites: methotrexate (MTX), azathioprine (AZA), and mycophenolate mofetil (MMF) are antimetabolites used to treat autoimmune disorders (e.g. rheumatoid arthritis, systemic lupus erythematosus, and psoriatic arthritis), and also are used to prevent rejection

of organs after transplantation (AZA and MMF). Other than their approved uses, these agents also are used in other rheumatologic conditions. MTX has been the most widely studied cytotoxic drug for pulmonary and extrapulmonary sarcoidosis [2■]. The efficacy of MTX has also been demonstrated in cutaneous, ocular, musculoskeletal, and neurologic sarcoidosis [4]. Therefore, MTX is often the first DMASD used in sarcoidosis. Compared to MTX, AZA has demonstrated a similar efficacy in pulmonary and extrapulmonary sarcoidosis.

Vorselaars *et al.* [5■■] recently compared the effects of second-line AZA with MTX on prednisone tapering, pulmonary function, and side-effects. In this international retrospective cohort study ($n = 200$), 55 patients received AZA and 145 patients received MTX. The investigators reported a similar steroid-sparing capacity for MTX and AZA, with the prednisone daily dose decreasing by 6.32 mg per year ($P < 0.0001$) on either therapy. Of patients who received at least 1 year of therapy, 70% tapered their daily prednisone dose by at least 10 mg. For these patients, the mean forced expiratory volume in 1 s (FEV1) increased by 52 ml per year ($P = 0.006$). The mean increase in vital capacity was 95 ml per year ($P = 0.001$) and in diffusion capacity of lungs (DLCO) (% predicted) was 1.23% per year ($P = 0.018$). Side-effects were similar in both treatment groups, with the exception of infections, which developed in a significantly higher percentage of patients receiving AZA vs. MTX (34.6 vs. 18.1% $P = 0.01$). Given these results, Vorselaars *et al.* [5■■] concluded that both AZA and MTX have substantial steroid-sparing capacities, a positive effect on lung outcomes, and comparable side-effect profiles, except for a higher rate of infections with AZA.

MMF, a potent immunosuppressive agent, is an inosine monophosphate dehydrogenase inhibitor that has an antiproliferative effect on lymphocytes and profoundly attenuates the production of autoantibodies by B cells [6]. Brill *et al.* [7] recently evaluated MMF as a steroid-sparing agent in patients with chronic pulmonary sarcoidosis. The investigators retrospectively investigated the efficacy of more than 6 months of MMF (median duration of treatment, 31 months) and systemic corticosteroids in 10 patients with biopsy-proven pulmonary sarcoidosis. Half of the participants initiated MMF because of side-effects of prednisone. The other half began MMF after not achieving an adequate response to prior therapy. During the study, patients significantly reduced daily corticosteroid doses, from 14.3 to 6.5 mg/day. In addition, four patients experienced a reduction in pulmonary symptoms and radiological signs, as well as improvements in pulmonary function. The other six patients' disease remained stable. Combining MMF with systemic corticosteroids did not cause any severe adverse events. On the basis of these findings, the investigators concluded that adding MMF to corticosteroids is feasible in chronic pulmonary sarcoidosis [7].

Leflunomide (LEF): this is an oral dihydroorotase inhibitor that has been approved by the FDA since 1998 to treat rheumatoid arthritis and is often used as an alternative to MTX. In sarcoidosis, it is used in addition to or as an alternative to MTX, based on data from observational studies, which have been reviewed elsewhere [2■]. Concerning adverse effects of LEF are emaciation and severe weight loss.

In patients with sarcoidosis, LEF causes similar toxicities to MTX. It has been associated with lower respiratory infections, hypertension, and peripheral neuropathy. Pulmonary toxicity also has been reported, but at a lower rate than with MTX. Patients with sarcoidosis who develop intractable cough while receiving MTX have been successfully treated with LEF, with symptom resolution reported [2■]. A recently reported safety signal with LEF is silent fibrosis. Lee *et al.* [8] reported that patients with rheumatoid arthritis who received concomitant LEF and MTX for more than 6 months had an increased risk of silent liver fibrosis. In this study, patients received LEF concomitantly with a dose of 10 or 20 mg of MTX. Of note, this study focused on patients with rheumatoid arthritis, a condition for which MTX is typically used at a higher dosage than in sarcoidosis. These findings therefore may not apply to this population. However, we suggest that patients with sarcoidosis who receive LEF should be monitored for this reaction, and combining these agents should be avoided.

Antimalarials

Antimalarials: Antimalarial agents, such as chloroquine and hydroxychloroquine, have demonstrated efficacy in sarcoidosis, most likely as a result of their immunomodulatory properties. Chloroquine has shown benefit in the treatment of pulmonary sarcoidosis, as reviewed elsewhere [1■], but chloroquine and hydroxychloroquine are mostly effective for cutaneous sarcoidosis.

Third-line therapy

TNF-α antagonists: TNF-α is a cytokine that contributes to cell-mediated immune responses and has been implicated in granuloma development in sarcoidosis and other diseases. In sarcoidosis specifically, TNF-α expressed by alveolar macrophages triggers the formation of granulomas and sustains their existence [9].

TNF-α inhibitors have demonstrated efficacy in sarcoidosis, especially in patients refractory to other treatments. A prospective, observational study [10■] evaluated the effects of adalimumab in 10 patients with refractory sarcoidosis by measuring disease activity using fluorodeoxyglucose-positron emission tomography (FDG-PET). Over 24 weeks, patients received corticosteroids and antimetabolites, as well as adalimumab 40 mg subcutaneously every other week. The standardized uptake value (SUV) was measured prior to treatment and 24 weeks later. The investigators reported that sarcoidosis disease activity, as measured by the SUV, significantly decreased in 9 of 10 patients ($P = 0.011$). The maximum median SUV decreased from 14.1 to 7.0 ($P < 0.03$). Patients with pulmonary sarcoidosis ($n = 6$), as evidenced by FDG uptake in the lungs, had decreasing uptake with adalimumab over time ($P = 0.035$). Disease activity also decreased in five of six patients with lymph node involvement ($P = 0.035$). Four patients had nonlymphatic extra-thoracic uptake, which decreased after treatment ($P = 0.05$). Despite the reductions in disease activity observed, adalimumab did not improve pulmonary function tests [10■].

In a different study, Russell *et al.* [11■] investigated the sustainability of infliximab response in 26 patients with pulmonary and extrapulmonary sarcoidosis for up to 85 months. Of the organs evaluated, 58.5% achieved improvement with infliximab via pulmonary

imaging ($P \leq 0.001$). On the basis of these findings, Russell *et al.* concluded that infliximab has the capacity to maintain improvements in sarcoidosis over time. Baughman *et al.* [12] conceived a phase 2 clinical trial investigating infliximab in 138 patients with chronic pulmonary sarcoidosis. Patients treated with infliximab achieved a statistically significant improvement of 2.5% of the predicted forced vital capacity (FVC). However, other secondary endpoints did not differ between the treatment groups, confounding the significance of the findings. One important limitation of the study was that only patients with stable disease were included, whereas findings from a post hoc analysis suggested that patients with severe disease might benefit from this drug.

Several additional studies of TNF-α inhibitors in sarcoidosis have been reported. A study of 26 patients with sarcoidosis who had refractory posterior uveitis [13] demonstrated the effectiveness of adalimumab in 22 (85%) patients, with an additional four (15%) patients achieving stable disease. In this study, extraocular symptoms (fatigue and DLCO) also improved and dosages of corticosteroids and MTX could be significantly reduced. An interesting study by Elfferich *et al.* [14] followed 343 patients with self-reported cognitive failure (concentration difficulties and memory loss) and fatigue associated with sarcoidosis. TNF-α inhibitors were associated with significant improvements on the Cognitive Failure Questionnaire and Fatigue Assessment Scale compared to corticosteroids with or without MTX and with no treatment.

Despite the potential utility of TNF-α inhibitors in sarcoidosis, the use of these agents in other diseases paradoxically has been associated with sarcoidosis or sarcoid-like granulomatosis (SLG) developing. At least 47 cases have occurred. Fortunately, the prognosis is good, with 37 of 47 patients experiencing complete resolution of the event after discontinuation [15,16].

Also concerning is the incidence and severity of tuberculosis (TB) in patients receiving TNF-α inhibitors. To help reduce the incidence of TB, guidelines recommend screening for TB in patients being considered for TNF-α inhibitors. Redelman-Sidi and Sepkowitz [17] recently reviewed the feasibility of screening for TNF-α inhibitors using interferon-gamma release assays (IGRAs). Their findings revealed that IGRAs, and specifically the T-SPOT.TB (Oxford Immunotec, Abingdon, UK) assay, have advantages over tuberculin skin test (TST) in some circumstances. For example, patients taking corticosteroids may benefit from the T-SPOT.TB assay [17].

For patients with sarcoidosis, we recommend using T-SPOT.TB first, given the booster effect of TST on IGRAs. A TST outcome of at least 5 mm should be considered positive if the patient takes prednisone 15 mg/day or its equivalent for at least a month. In treatment-naïve patients who are not immunosuppressed, a TST of at least 10 mm is a positive test. Either positive test warrants an extensive investigation for active TB. If there is no evidence of active TB, treatment for latent TB should be started at least 4 weeks before starting therapy. The authors conclude that convincing data for available latent TB tests are lacking and more prospective studies are needed to help improve their accuracy.

Rituximab: this chimeric monoclonal antibody that targets CD20 considerably reduces the number of mature B lymphocytes in circulation [18]. The efficacy of rituximab in pulmonary sarcoidosis has been reviewed [2■]. Several case reports also have highlighted the efficacy of rituximab as a treatment for ocular sarcoidosis [19].

Other agents

The efficacy of several other agents in pulmonary sarcoidosis has been demonstrated. For example, the efficacy of pentoxifylline, a phosphodiesterase inhibitor, in treating acute pulmonary sarcoidosis was recently reviewed [2■]. Inhaled vasoactive peptide is another agent that might be beneficial, as recently reviewed by Baughman and colleagues [2■]. However, as the reviewers pointed out, no changes in pulmonary function tests have been demonstrated [2■].

An interesting study by Julian *et al.* [20■■] reported the effects of nicotine on pulmonary sarcoidosis. Thirteen patients with symptomatic sarcoidosis received conventional therapy with or without nicotine treatment. The reaction of blood cells to ligands for certain Toll-like receptors (TLRs) was assessed. TLR-2 and TLR-9 responsiveness was restored in nicotine-treated individuals. Additional research is needed to confirm these data.

EXTRAPULMONARY SARCOIDOSIS

Although sarcoidosis most frequently affects the lung, any other organ can also be affected. In this section, we review the current data about medications that have successfully been used to treat extrapulmonary sarcoidosis. As with pulmonary sarcoidosis, data from prospective clinical trials are sparse [21]. The decision to treat patients with extrapulmonary manifestations is difficult as physiological functions are often not compromised and diagnosing ‘systemic sarcoidosis’ involves the use of imaging techniques. The most frequent extrapulmonary manifestations affect the lymph nodes, eyes, skin, liver, musculoskeletal system and, rarely, the central nervous system, kidneys, or the heart. As such, extrapulmonary involvement occurs at a frequency ranging from less than 5 to 30% in sarcoidosis.

First-line therapy: corticosteroids

As in pulmonary sarcoidosis, corticosteroids are still considered the mainstay of treatment for extrapulmonary sarcoidosis. The usual dosing range for corticosteroids in the treatment of extrapulmonary sarcoidosis is 20–40 mg/day, with tapering to the lowest effective dose an ultimate treatment goal [1■]. However, because of their long-term toxicity, alternative corticosteroid-sparing treatment agents are sometimes needed, as are second-line and thirdline options for refractory cases.

Second-line therapy: disease-modifying antisarcoid drugs

The same second-line agents listed for pulmonary sarcoidosis, MTX, AZA, MMF, LEF, cyclophosphamide, and antimalarials, all have been used to treat extrapulmonary manifestations of sarcoidosis as well. Our knowledge of these agents mainly comes from retrospective clinical trials or case reports, which makes treatment decisions difficult. For

example, the retrospective trial that compared MTX and AZA as second-line agents for pulmonary and extrapulmonary manifestations was described previously [5■■]. Both drugs were effective steroidsparing agents, but more infections were reported with AZA. Data from several case reports also suggest effectiveness of MTX for cutaneous [22], oral [23], and skeletal [24] sarcoidosis.

Hydroxychloroquine also has been used for the treatment of extrapulmonary sarcoidosis. There are no new data from clinical trials that evaluated the use of hydroxychloroquine, but case reports suggest that treatment might be most useful for cutaneous manifestations [25,26].

The effectiveness of LEF was examined in one retrospective trial and showed a complete or partial response for cutaneous, ocular, and sinonasal involvement, but LEF was less effective for neurological and musculoskeletal manifestations [27].

MMF has been used for few sarcoidosis manifestations. The most convincing data show that it might have a role in neurosarcoidosis (affecting the central nervous system), in which it demonstrated efficacy with a low risk for the side-effects reported [28].

Cyclophosphamide is a well established immunodepressant, known to influence cell cycle and DNA synthesis. It also has demonstrated a capacity to suppress both humoral and cellular immunity [29]. Its immunosuppressive and anti-inflammatory effects arise from the decrease in lymphocyte number and function that ensues after exposure to cyclophosphamide.

In a meta-analysis of studies that investigated the utility of cyclophosphamide in scleroderma-related interstitial lung disease, cyclophosphamide did not prevent deterioration of lung function (i.e., DLCO) after 12 months [30]. In sarcoidosis, cyclophosphamide is typically used for cardiac sarcoidosis or neurosarcoidosis.

Adverse events related to cyclophosphamide mainly include nausea and vomiting, which are generally mild. However, permanent discontinuation may be necessary in patients who experience major adverse effects, like hemorrhagic cystitis, recurrent pneumonia, intolerable nausea, and elevations in liver enzymes [30]. It also poses the risk of ovarian failure to women of reproductive age. In some of these cases, infliximab is preferred and probably superior to cyclophosphamide [1■].

A new phosphodiesterase inhibitor, apremilast, has recently demonstrated efficacy in chronic cutaneous sarcoidosis, but has not yet been examined in the treatment of pulmonary sarcoidosis [31].

Third-line therapy: tumor necrosis factor-α antagonists

Some cases of extrapulmonary sarcoidosis might require additional therapy after other agents have failed or individual intolerance to second-line agents. Of the TNF-α inhibitors available, infliximab and adalimumab are the best studied in refractory sarcoidosis. As mentioned previously, Russell *et al.* [11■] demonstrated the effects of infliximab in patients with pulmonary and extrapulmonary sarcoidosis refractory to conventional therapy.

Infliximab was effective in improving organ dysfunction in about 60% of patients treated. No significant adverse events leading to discontinuation of the agent were reported. Knopf *et al.* [32] showed effectiveness of adalimumab in two patients with head and neck sarcoidosis refractory to corticosteroid treatment. In one case, sarcoidosis-associated vasculitis was successfully treated with adalimumab [33]. A patient who developed diabetes insipidus because of neurosarcoidosis recovered after therapy with infliximab [34]. Taken together, we conclude that TNF-α inhibitors might be a valuable treatment option for patients refractory to conventional therapy. However, they should be used with caution for the aforementioned reasons [15].

Other agents

NSAIDs are mainly used to treat patients with Löfgren's syndrome, meaning the triad of bihilar lymphadenopathy, erythema nodosum, and bilateral arthritis of the ankle. For many patients, NSAIDs are all that is required to control the disease, whereas other patients might need additional corticosteroids.

Antioxidants, such as querceptin, have also been studied in sarcoidosis [35■]. Querceptin, which belongs to the flavanoid family, was administered to 12 of 18 patients with sarcoidosis in a small study. Querceptin supplementation showed a reduction in markers of oxidative stress (malondialdehyde) and inflammation (expressed as reduced ratios of TNF-α/IL-10 and IL-8/IL-10). These findings were more pronounced in patients with higher basal levels of suggestive markers [35■]. In our view, these findings merit assessment in larger trials with clinical endpoints.

Special situations

Small-fiber neuropathy (SFN): this difficult to diagnose and treat complication of sarcoidosis with prevalence ranging from 40 to 60% needs a different approach as conventional therapy usually does not work. A first case report demonstrated effectiveness of infliximab in this condition [36], supporting the concept that SFN is, at least in part, mediated by elevated TNF-α levels. In a recent review, Heij *et al.* [37] summarized the treatment options for SFN, which mainly consist of treatment addressing the neuropathic pain. Antidepressants, anticonvulsants, topical anesthetics, and opioids are used for symptom relief, but unfortunately are only effective in about 50% of patients. Intravenous immunoglobulins have also been used with some success in this condition.

A novel approach has been the administration of ARA 290, a peptide developed to activate the innate repair receptor. Activation of this receptor by ARA 290, which, in short, is derived from the three-dimensional structure of erythropoietin, enhances anti-inflammation and tissue protection downstream. Heij *et al.* [38■] reported that ARA 290 was well tolerated and efficacious in patients with sarcoidosis suffering from SFN. Twelve of twenty-two patients received ARA 290 three times a week at a dose of 2 mg for 4 weeks. Statistically significant improvements in the small-fiber neuropathy screening list (SFNSL) scores were noted. Symptom severity rather than frequency was attenuated as were symptoms of autonomic dysfunction. No safety concerns were raised, thus making ARA 290 an attractive and possible treatment option for SFN.

Sarcoidosis-associated fatigue (SAF): a total of 50–70% of patients with sarcoidosis suffer from SAF. The most important step is to identify treatable causes of SAF, such as diabetes or hypothyroidism. Fatigue can be a side-effect of the treatment itself, mainly of corticosteroids. SFN and dyspnea also have been associated with SAF, as reviewed by Drent *et al.* [39]. In the same review treatment options were summarized, with the most robust data for neurostimulants such as methylphenidate and neurostimulant-like drugs such as armodafinil, a drug used to treat daytime somnolence and narcolepsy. Case series also have described some effectiveness of TNF-α antagonists.

CONCLUSION

Given the data reviewed herein, we recommend initiating treatment for both pulmonary and extrapulmonary sarcoidosis based on the compromised organ function and index organ involvement causing symptoms and progressive organ dysfunction, taking into consideration the number of affected organs seen on physical examination, as well as the presence of inflammatory markers and concomitant autoimmune disorders or other comorbidities. Table 1 summarizes our recommendations. In the first-line setting, we recommend corticosteroids, with the goal of eventually tapering the dose and discontinuing corticosteroids altogether. Administration of DMASDs should be reserved for patients refractory to corticosteroids or those with contraindications to corticosteroids because of toxicity or lack of efficacy. For such cases, MTX should be the first agent initiated, as it has been the most extensively studied, with the best benefit–risk profile. For patients with mild cutaneous lesions, hydroxychloroquine should be considered either as a monotherapy or in combination with other DMASDs. AZA, LEF, and MMF should be considered in patients intolerant to MTX.

Biologics can be an effective alternative for patients with progressive disease or after DMASD failure. However, it should be recognized that these agents can also induce sarcoidosis; in a subset of patients, biologic therapy using TNF-α inhibitors may be considered.

Using a translational approach to study this heterogeneous disease will provide the tools to identify patients with pulmonary and extrapulmonary disease at risk of progression and who may benefit from aggressive nonsteroidal therapy. As implied throughout this review and in many other published reports, sarcoidosis is not one disease; rather, it is an assorted group of conditions. Therefore, treatment should be highly individualized until we have more robust guidelines based on the translational clinical trial approach.

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REFERENCES AND RECOMMENDED READING

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KEY POINTS

- The decision to treat pulmonary and extrapulmonary sarcoidosis should depend on patient symptomology and the extent of compromised organ function.
- Corticosteroids remain the treatment of choice for most patients with pulmonary and extrapulmonary sarcoidosis.
- Disease-modifying antisarcoid drugs and biologics should be reserved for second-line or third-line treatment after other therapies or as steroid-sparing agents for patients with chronic disease.

Table 1
Treatment recommendations for sarcoidosis

	First line	Second line	Third line
Pulmonary	Corticosteroids	MTX AZA	TNFi RTX VIP? Antioxidants?
Extrapulmonary			
Ocular	Corticosteroids	MTX AZA? LEF	TNFi
Cutaneous	Corticosteroids	HCQ LEF MTX? AZA?	Apremilast?
Lymph node	Corticosteroids	MTX LEF? AZA?	TNFi?
Musculoskeletal	Corticosteroids NSAID	MTX HCQ AZA?	TNFi
Neurosarcoidosis	Corticosteroids	MTX AZA CYC MMF?	TNFi?
Cardiac	Corticosteroids	MTX AZA CYC LEF?	TNFi?
Renal	Corticosteroids	AZA HCQ TNFi?	
Small-fiber neuropathy		TNFi IVIG ARA 290	
Sarcoidosis-associated fatigue	Treat sarcoidosis activity Rehabilitation	Methylphenidate Armodafinil CBT	TNFi?

AZA, azathioprine; CBT, cognitive-behavioral therapy; CYC, cyclophosphamide; HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulins; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; TNFi, tumor necrosis factor alpha inhibitors; VIP, vasoactive intestinal peptide.