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Refractory pulmonary sarcoidosis – proposal of a definition and recommendations for the diagnostic and therapeutic approach

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Abstract

Patients with sarcoidosis undergo spontaneous remission or may be effectively controlled with glucocorticoids alone in many cases. Progressive and refractory pulmonary sarcoidosis constitute more than 10% of patients seen at specialized centers. Pulmonary fibrosis and associated complications, such as infections and pulmonary hypertension are leading causes of mortality. No universal definition of refractoriness exists, we therefore propose classifying patients as having refractory disease when the following criteria are fulfilled: (1) progressive disease despite at least 10 mg of prednisolone or equivalent for at least three months and need for additional disease-modifying anti-sarcoid drugs due to lack of efficacy, drug toxicity or intolerability and (2) treatment started for significant impairment of life due to progressive pulmonary symptoms. Both criteria should be fulfilled. Treatment options in addition to or instead of glucocorticoids for these patients include second- (methotrexate, azathioprine, leflunomide) and third-line agents (infliximab, adalimumab). Other immunomodulating agents can be used, but the evidence is very limited. Newer agents with anti-fibrotic properties, such as pirfenidone or nintedanib, might hold promise also for the pulmonary fibrosis seen in sarcoidosis. Treating physicians have to actively look for potentially treatable complications, such as pulmonary hypertension, cardiac disease or infections before patients should be classified as treatment-refractory. Ultimately, lung transplantation has to be considered as treatment option for patients not responding to medical therapy. In this review, we aim to propose a new definition of refractoriness, describe the associated clinical features and suggest the therapeutic approach.

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pulmonary sarcoidosis; biological agents; corticosteroids; interstitial lung disease

Introduction

Sarcoidosis is a multisystem disease characterized by the presence of non-caseating granulomas that affects the lungs in over 90% of patients (1). The disease pathogenesis has not been completely elucidated. However, our current understanding is that it likely includes exposure to one or more, possibly airborne-transmitted antigens (bacterial, organic, anorganic), which then trigger an abnormal immune response in a genetically predisposed host (2). About two thirds of patients will undergo remission within several months to a few years, whereas about one third will require short- or long-term treatment (1). The intriguing observations of chest radiographs in sarcoidosis published by Scadding in 1961 (3) are still considered the gold standard because of the limited use of radiation and its association with resolution or progression of the disease. However, inter- observer variability and lack of association with functional clinical parameters (e. g. pulmonary function tests, six minute walk test) are limiting factors (4). Computed chest tomography (CT) has been found useful in distinguishing areas of potentially reversible lung damage from areas of presumed fibrotic lung (4). Even more importantly, chest CT with or without contrast often allows for the identification of mediastinal or hilar adenopathy, allowing for a potential diagnosis of sarcoidosis via endobronchial ultrasound (EBUS) guided transbronchial needle aspiration. It thereby prevents the need for mediastinoscopy in as many as 87% of patients (5). Especially in patients with parenchymal disease and higher risk for complications, such as pneumothorax, EBUS alone may yield a diagnosis and obviate the need for transbronchial biopsies (6).

Treatment recommendations do exist for pulmonary and extra-pulmonary manifestations of sarcoidosis (7–10), however, the available evidence to guide treatment is limited. Therapeutic options include first-line (glucocorticoids), second-line (disease-modifying anti-sarcoid drugs, DMARD) and third-line (biological agents) therapies. Treatment should always be tailored to the individual patient and adapted to the presence or absence of clinical symptoms or worsening of objective functional parameters, such as pulmonary function tests.

Refractory disease has not been universally defined and treatment recommendations are not existent for this, albeit small, group of patients. In addition, it is challenging to define refractory disease with no approved therapies other than glucocorticoids (and Acthar gel, which has been approved based on very limited evidence) by the U. S. Food and Drug Administration and because of the systemic nature of the disease. In specialized centers, refractory or progressive patients can nevertheless constitute a significant proportion of all patients. In a survey from a World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) Task Force, more than 10% of patients required and increase in systemic medication 5 years after the initial diagnosis (11). Data from the ACCESS studies revealed that among all characteristics of the included patients, dyspnea and need for initial

systemic therapy were associated with systemic therapy at two years of follow-up (12). In addition, organ involvement is different according to race, sex and age. African Americans, for example, tend to have more skin involvement (other than erythema nodosum), hematological abnormalities as well as lymph node, liver and bone marrow affection (13). However, it is important to note that organ involvement *per se* does not necessarily translate into chronicity or refractoriness.

Also, it is clear that refractory sarcoidosis often includes significant fibrosis. Fibrotic sarcoidosis is associated with increased mortality (14,15). Patients in this group die not only from progression of their inflammatory disease, but also from complications of the fibrosis, including pulmonary hypertension (PH) and infections (15).

The overlapping, but nevertheless different concept of “advanced pulmonary sarcoidosis” has evolved over the last couple of years (16). Advanced pulmonary sarcoidosis includes fibrocystic changes with either airflow limitation or severe restrictive impairment and can harbour active or inactive lesions (as evidenced by 18F-positron emission-computed tomography (PET-CT)). The associated complications include chronic respiratory insufficiency, pulmonary hypertension, pulmonary aspergillosis or other infections (16). Acute worsening events are frequent with a median of three episodes per year (17). Advanced pulmonary sarcoidosis can be seen as potential cause of treatment-refractory disease and the aforementioned complications have to be actively looked for.

In this review, we aim to define treatment-refractory disease, propose clinical and functional parameters associated with refractoriness and, ultimately, suggest a step-wise approach for the management of refractory patients.

Methods and search strategy

Pubmed and Google scholar were searched using the terms “refractory sarcoidosis”, “progressive sarcoidosis”, and combinations of “sarcoidosis” and “methotrexate, azathioprine, leflunomide, rituximab, infliximab and adalimumab”. Articles were reviewed by abstract and included when deemed appropriate by at least two authors. Additional references were identified from included articles and personal archives of the authors. Reviews, case series and clinical studies published in peer-reviewed journals were included. Articles published in English, Spanish and German were included for analysis. Non-english language articles were reviewed and translated by one author (PK) and their content discussed with at least one other author (KS, RPB or NJS). These articles were also included when at least two authors agreed upon their appropriateness.

Definition of refractory pulmonary sarcoidosis

In our article we strive to characterize the term refractory (that is: treatment-refractory) pulmonary sarcoidosis. As of yet no universally accepted definition of refractory pulmonary sarcoidosis exists. However, patients with progressive disease despite adequate therapy consisting of corticosteroids are commonly referred to as having refractory disease according to the literature (18). While corticosteroids remain the first line of treatment and are being used as such, no validated protocol exists with regard to dosage or treatment

duration, thereby complicating what is to be considered as treatment refractory (1,19,20). A systematic review from 2005 found that dosages vary widely and that no clear evidence of benefit exists beyond two years of treatment (21). Indications for therapy, response and thereby optimal treatment duration are especially difficult to measure when looking at quality of life rather than objective evidence of organ dysfunction. However, validated questionnaires exist (e. g. Sarcoidosis Health Questionnaire and Fatigue Assessment Scale) and guidelines on their use have been published (22). Factors confounding assessment of response to therapy are coexistence of other diseases or complications due to immunosuppressive therapy. It becomes clear that along with the question on how to define refractory sarcoidosis, one must aim to answer questions about what the optimal dose and duration of a treatment ought to be and how to assess its response.

In light of this complex background we propose the following definition of refractory pulmonary sarcoidosis:

1. Progressive pulmonary disease despite glucocorticosteroid therapy at adequate dosage defined as at least 10 mg of prednisone (23) once a day and duration of therapy of at least 3 months after initial dosages of 20–40 mg per day for 1–3 months and need for additional therapy due to lack of efficacy, glucocorticoid toxicity or severe side effects
2. Treatment started for impaired quality of life due to progressive pulmonary symptoms with or without additional disease manifestations (e.g. disfiguring disease, neurosarcoidosis, etc.)

To be considered as treatment-refractory, pulmonary disease patients should fulfill both criteria and other causes such as pulmonary arterial hypertension, infection or cardiac sarcoidosis have to be excluded.

This definition is based on similar descriptions of refractory pulmonary sarcoidosis in the literature and aims to simplify the approach to any given patient. In addition, it is the authors' personal experience and by no means a recommendation which is based on solid evidence, that patients fulfilling these criteria are those that are usually more difficult to treat in clinical practice. While there are no standardized end-points to define refractoriness, it is the authors' intention to propose a definition which serves clinicians as a guideline on when to intensify treatment. Clearly, this definition has to be validated in well-designed clinical trials.

Features associated with refractory disease

As many as 10% of patients undergoing treatment for sarcoidosis will continue to have active disease (18). Most deaths from sarcoidosis in the western hemisphere occur because of advanced pulmonary fibrosis with pulmonary arterial hypertension (PAH) and less commonly cardiac, central nervous system (CNS) and hepatic involvement (24,25). This contrasts with reports from Japan citing cardiac complications as cause of death in 77% to 85% of sarcoidosis-related deaths as recently reviewed by Lynch *et al.* (26). Given the high rate of pulmonary involvement and potential of progression to end-stage fibrosis we will focus our review on the diagnosis of pulmonary refractory sarcoidosis and describe clinical

findings that could constitute refractoriness (Table 1). Finally, we will propose a diagnostic and therapeutic algorithm for refractory pulmonary sarcoidosis patients (Figure 1).

Clinical symptoms

Symptoms of mediastinal-pulmonary sarcoidosis can encompass a large range of clinical findings. The most common symptom is a persistent cough, followed by dyspnea (which is rare early in the disease course) and rarely chest pain, wheezing or hemoptysis. Crackles on exam are rare and correlate with changes of fibrosis. The variety in clinical symptoms is mirrored in the wide range of histopathological and radiographic presentations. However, these objective and subjective data do not always correlate.

Patients considered to have refractory disease will typically have persistent symptomatology (dyspnea, cough etc.) despite an adequate therapeutic trial with glucocorticoids (see definition above). Sarcoidosis patients who respond well to higher (20–40 mg per day) glucocorticoid doses at first but have recurrent symptoms upon reduction to targeted doses of less than 10 mg per day after three months will also be candidates for the introduction of a second-line agent and thus meet the definition of “treatment-refractory”. The presence of additional progressive extra-pulmonary symptoms requiring immunosuppressive treatment in a situation of stable pulmonary disease would also constitute systemic refractory sarcoidosis stratified by the index organ involved.

Non-invasive testing (Pulmonary function testing and 6-minute walk distance)

There is no diagnostic pattern in PFTs and the volume of forced vital capacity (FVC) does not correlate clinically with symptoms of dyspnea (27). The most prevalent pattern of pulmonary function tests (PFTs) in patients with sarcoidosis is restrictive (36, 37). Obstruction can nevertheless also be present, either in isolation or concomitantly (29–31). This correlates with the histopathological pattern of sarcoidosis either involving the lung parenchyma, the airways or both. Obstruction in sarcoidosis may be less responsive to immunosuppressive therapy (32) and can be a significant source of refractory disease. In sarcoidosis, there is no definite consensus on how to follow changes in FVC in response to treatment (28). In idiopathic pulmonary fibrosis (IPF), it was shown that a decline of 5% or more was associated with an increase in mortality (33) and a decline of 2–6% has been found to represent the minimal clinically important difference (34). While these thresholds may not necessarily hold true for sarcoidosis, we suggest that, in the absence of better data, a decline of 5% (absolute change of predicted) FVC is consistent with refractoriness in sarcoidosis patients. The caveat to this approach is the test variability and the impact of obesity and long-term use of glucocorticosteroids as well as the presence or absence of sleep apnea on the testing. Our unpublished data suggest that a significant reduction in DLCO may indicate refractory pulmonary disease in the absence of PAH as a cause of drop in DLCO.

The 6-minute walk distance (6MWD) is an established measurement in many pulmonary conditions. Although sarcoidosis is not listed as an indication for testing by the American Thoracic Society (35), it has nevertheless been used in this population (36). While results (improvement or lack of improvement) have been mixed in clinical trials which incorporated

it as outcome measure, refractory patients should either have declining values as compared to baseline or increase only with supplemental oxygen. One has to keep in mind, however, that the 6MWD is influenced by multiple factors, making it difficult to discriminate the cause of declining values in some cases (36).

Role of imaging in refractory pulmonary Sarcoidosis

Many patients who respond readily to glucocorticoid treatment alone may never need advanced imaging in addition to conventional chest radiographs. Those patients who have persisting or worsening clinical symptoms and functional findings despite adequate treatment will require computed chest tomography or other imaging modalities.

Studies that evaluated the CT features that are associated with sarcoidosis aimed to differentiate reversible features such as nodules or peribronchovascular thickening from findings of potentially irreversible damage such as honeycombing, bronchial distortion or bullae (28, 29). Prior to intensifying therapy in a patient nonresponsive to corticosteroids we recommend evaluating for CT scan findings suggestive of end stage fibrosis, possibly followed by a PET scan to screen for sites of active inflammation. The suspicion of fibrotic changes would be supported by stable PFTs over several years (38). CT is also the most important imaging modality to assess for complications of advanced pulmonary sarcoidosis, such as aspergilloma, pulmonary hypertension or obstruction (4). In a recent study, Walsh and colleagues applied a staging system combining fibrosis grading in high-resolution computed tomography (HRCT) and the composite physiological index (CPI) to a sarcoidosis population (14). This staging system was found to be predictive of mortality and could easily be used by radiologists and clinicians likewise.

A newer imaging modality correlating with inflammatory activity is ^{18}F -FDG-PET. It may especially predict worsening of pulmonary involvement as well as show areas of active disease involvement, expected to improve with treatment. Not all insurances cover ^{18}F -FDG-PET in sarcoidosis (39–43). ^{18}F -FDG PET has been shown to demonstrate active inflammation even in stage IV CXR, thereby being a useful marker of active disease and potential response to therapy (42).

All patients suspected of having refractory pulmonary sarcoidosis should receive imaging by CT assessing for reversible/irreversible including clinico-radiological staging as proposed by Walsh et al. If irreversible features are identified, we suggest the consideration of ^{18}F -PET-CT to look for active lesions which could be amenable to treatment. If no active lesions are identified, complications need to be addressed and treated. Nevertheless, even in inactive sarcoidosis by imaging, a therapeutic trial with second-line agents might be justified for individual patients. Prospective validation studies are required to evaluate the role of CT and PET in predicting the need for aggressive therapy in refractory disease.

Biomarkers

Biomarkers as a measurement of disease activity have not yet been incorporated in clinical practice, but are being investigated. Examples include soluble interleukin-2 receptor (sIL2-R), chitotriosidase and exhaled neopterin (44). Angiotensin-converting enzyme (ACE) has

not been found to reliably correlate with disease activity (45), which might be due to different genotypes influencing ACE levels (46). Furthermore, treatment with corticosteroids influences ACE levels. Nevertheless, serial measurement of ACE and sIL2-R levels were found to be useful in individual patients to monitor treatment effects (47). Interestingly, measurement of serum amyloid has been found to correlate with disease activity in pulmonary sarcoidosis (48). However, its current use in clinical practice can not yet be recommended. In an interesting study with small sample size, an unbiased 20-gene signature was found to be superior to a more restrictive 31-gene T-cell receptor signaling profile in peripheral blood to distinguish complicated from uncomplicated sarcoidosis (49). Complicated sarcoidosis in this study was defined as cardiac, neurologic or severe pulmonary sarcoidosis. The fact that the T-cell receptor signaling centered gene expression profile was inferior compared with the gene signature derived from genome-wide peripheral blood gene expression analysis underlines the fact that the pathogenesis of sarcoidosis might be T-cell driven, but refractoriness might involve more complex mechanisms (49). In summary, we recommend serial measurements of ACE and/or sIL2-R at baseline and to monitor treatment response when baseline levels were elevated.

Additional biomarkers are under investigation. Peripheral blood lymphocytopenia has been found to correlate with severity of disease manifestations, including pulmonary sarcoidosis (50). In addition, C-reactive protein levels have been found to indicate more a more severely affected subgroup of patients. Interestingly, these patients may have better responses to Infliximab when this treatment is indicated (51). Experimental studies identified additional cytokines that might be important in the disease pathogenesis and different phenotypes. Interleukin(IL)-7 (increased) and IL-5 (decreased) have been found to be altered compared to healthy controls. IL-5 was significantly more decreased in non-fibrotic pulmonary sarcoidosis patients, IL-7 was increased in the fibrotic phenotype, but not statistically significant (52). While still experimental, these results might identify different phenotypic subsets of sarcoidosis patients. All these biomarkers, however, still have to be validated in translational clinical studies and have not been established in clinical practice as of yet. To conclude, patients with refractory disease are characterized by persisting or worsening clinical symptoms, decline of PFT despite treatment, and/or worsening of findings on imaging or changes from potentially reversible to irreversible features despite adequate doses of glucocorticoid treatment, keeping in mind that the adequate dose has been defined based on expert opinion and consensus rather than convincing evidence from clinical studies. No universal biomarkers which are useful in terms of diagnosis or response to treatment have been defined, ACE and sIL2-R are the most frequently used, given that levels are increased at baseline.

Our proposed diagnostic approach is depicted in the upper part of figure 1 and the clinical/ investigational findings associated with refractoriness are presented in table 1. In the next section, we will describe our therapeutic approach for patients with refractory disease.

Therapeutic options in refractory sarcoidosis

Glucocorticosteroids in doses ranging from 20 – 40 mg/day are the mainstay of treatment and effective in a majority of sarcoidosis patients with possible tapering to a maintenance

dose of < 10 mg/d within a few months. Acthar gel, an ACTH-analogue and FDA-approved medication, is not routinely used by sarcoidologists, since the evidence base is weak, but studies are ongoing to investigate its role in chronic pulmonary sarcoidosis (NCT 02188017). The clinician, often a pulmonologist or rheumatologist, will nevertheless encounter patients who do not readily respond to GC treatment and are therefore considered treatment-refractory.

We will focus the following section on additional, second- and third-line therapeutic agents to be considered in patients with refractory pulmonary sarcoidosis. The therapeutic approach to refractory sarcoidosis is summarized in the lower part of figure 1.

Second line disease modifying anti-sarcoid drugs

The evidence for using these agents including methotrexate (MTX), azathioprine (AZA), leflunomide (LEF), cyclosporine (CYA), antimalarials (hydroxychloroquine, HCQ, and chloroquine, CHQ) and mycophenolate mofetil (MMF) is astonishingly low-grade. Nevertheless, many physicians treating sarcoidosis patients have gained experience using these agents in sarcoidosis patients. The choice of which one to use depends on physician preference and the predominant organ involvement rather than objective evidence. We will summarize the existing evidence and our personal experience with the use of non-steroidal agents. Table 2 gives an overview of specific dose and monitoring recommendations.

Methotrexate is typically the first steroid-sparing agent used in sarcoidosis and its first reported use in a refractory sarcoidosis patient can be found in the literature as early as 1968 (53). Evidence for MTX use derives from one randomized double-blind placebo-controlled trial (54) and few open-label clinical trials (55–58), additional case series or singular case reports can be found numerously in the literature. In most studies, its use was associated with a possible dose-reduction of glucocorticoids and/or improvement in pulmonary function tests. In 2013, the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) has published recommendations for the use of MTX in sarcoidosis (59). The risk of hypersensitivity pneumonitis in sarcoidosis seems to be lower than in patients with rheumatoid arthritis, in which this side effect is estimated to occur in up to 5% of patients (7). In summary, the usual starting dose ranges from 5 – 15 mg / week with supplementation of folic acid of at least 5 mg / week.

Azathioprine has been studied only in open-label clinical trials (57,60,61) and one retrospective analysis (62) with mixed results. The open-label trials showed small improvements in forced vital capacity in a limited number of patients and steroid-sparing capacities and/or disease regression in 54% in one study (57). The retrospective analysis compared MTX *versus* AZA and found similar clinical benefits (prednisone dose reduction, improvement of FEV1 and VC) but more infectious complications with AZA (62). This important study provides evidence for the efficacy of both MTX and AZA in a larger number of patients in terms of steroid-sparing capacity and clinical improvement.

Leflunomide has been studied in pulmonary (and extra-pulmonary) sarcoidosis in two open-label trials (63,64) and has shown steroid-sparing properties in a standard dose of 20 mg/d. In one study, it improved forced vital capacity. Gastrointestinal side effects (nausea and

diarrhea) and elevation of hepatic enzymes were the most common side-effects. In our experience, loading with LEF (100 mg on three consecutive days) is usually not necessary. LEF can, however, cause interstitial lung disease (ILD). In a systematic review by Raj and Nugent (65), ILD caused by LEF was found most often within the first 3 months after initiation, the most common finding were bilateral ground glass opacities on chest CT and diffuse alveolar damage on histopathologic examination.

Other second-line agents are less commonly used according to the literature. Mycophenolate mofetil (MMF) has not been studied in detail in sarcoidosis. The first use in a sarcoidosis patient with refractory uveitis appeared in a paper published in the *Lancet* in 1998 (66). MMF has shown efficacy in severe cutaneous sarcoidosis in a case series reported by Kouba and colleagues in 2003 (67). In addition, there are few reports on its use for renal sarcoidosis (68). In a retrospective study of 37 patients with pulmonary sarcoidosis, MMF did not improve pulmonary function tests but was steroid-sparing in some patients (69). Its role for pulmonary sarcoidosis is therefore not clear as of yet.

The antimalarials hydroxychloroquine (HCQ) and chloroquine (CHQ) are thought to modulate immune response through inhibition of toll-like receptors-7 and -9 (70). There are limited data for their use in pulmonary sarcoidosis. In one randomized trial, maintenance therapy with CHQ was associated with slower deterioration of PFTs and fewer relapses (71). In a recent analysis, it was confirmed that the risk of retinopathy with prolonged use is higher depending on the cumulative dose (72). A dosage of HCQ of < 5 mg/kg actual body weight should be used and ophthalmologic evaluation at baseline and annually after five years is considered mandatory with their use (73).

Third-line biological agents

Experimental evidence and limited clinical studies suggest that influencing the abnormal immune response in sarcoidosis by biological agents might be useful in certain patients. However, one has to note that the results from clinical trials with different tumor necrosis factor- α blockers are conflicting despite a clear rationale. Data are available for the Tumor necrosis factor alpha blockers infliximab, adalimumab, etanercept and golimumab, the B-cell-depleting agent rituximab and the interleukin 12/23-antagonist ustekinumab. Additional immunomodulatory drugs, such as thalidomide, pentoxifylline and apremilast, are considered experimental and their role has yet to be defined. Data on biological and experimental agents were recently reviewed (7, 9), we will therefore focus this section on agents investigated in refractory pulmonary sarcoidosis.

Infliximab is the best studied biological agent in sarcoidosis. Over the last ten years, its efficacy has been reported in numerous case reports and retrospective studies of patients with severe pulmonary and extra-pulmonary disease. However, there are only two prospective, double-blind placebo-controlled randomized clinical trials for pulmonary sarcoidosis (74,75). These trials involved 138 and 19 patients, respectively, with chronic pulmonary disease despite glucocorticoid therapy. Infliximab led to improvement in forced vital capacity (FVC) and radiographical progression (74) or FVC alone (75). In addition, we found that patients with elevated C-reactive protein levels seemed to benefit more from the

intervention (51). Of note, the beneficial effects of Infliximab for extra-pulmonary sarcoidosis, including neurosarcoidosis, have been described in the literature despite the absence of higher quality clinical trials which are difficult to perform due to the very varied clinical presentations. In patients requiring prednisone doses higher than 15–20 mg, Infliximab has not been shown to improve the difference in FVC after two years of treatment (76).

Adalimumab is an alternative option and experiences derived from larger case series as well as results from open label clinical trials are encouraging. We recently published an open-label clinical trial (77) which involved 11 patients with refractory sarcoidosis. Treatment success was defined as improvements in FVC, 6MWD, Borg dyspnea score or possible reduction of concomitant medication. After 24 and 52 weeks, 9/11 (82%) and 8/11 (80%) had improved in at least one of the variables tested. Of practical importance, the dose use in this trial was 40 mg weekly, which is higher than the standard dose of 40 mg every other week approved by the FDA for rheumatoid arthritis.

The WASOG provides recommendations for the use of the TNF-blockers Infliximab and Adalimumab in sarcoidosis, these are, however, based on the limited data available and expert opinion of leading sarcoidologists (78). Recommendations regarding dosage (see also Table 2), discontinuation as well as general recommendations for the use of anti-TNF alpha blockers were formulated.

The trial for progressive pulmonary sarcoidosis including Etanercept, a soluble TNF receptor, was terminated prematurely due to ineffectiveness (79). However, occasional case reports have also noted efficacy for diverse disease manifestations (80).

A recent trial involving Ustekinumab, a combined anti interleukin (IL) 12/23 antibody, and Golimumab, a TNF alpha blocker, was designed to assess the clinical benefits in pulmonary and cutaneous sarcoidosis. The primary end-point, improvement of change in predicted percentage of FVC was not reached. There was a tendency of Golimumab to improve some of the cutaneous manifestations of sarcoidosis, but this did not reach statistical significance either.

Ultimately, Rituximab, a monoclonal antibody directed against CD20-positive B-cells, which is used in malignancies and many autoimmune diseases (including rheumatoid arthritis, vasculitis, refractory systemic lupus erythematosus, primary Sjögren's syndrome among many others) was reported as salvage treatment in cases of refractory disease. It was demonstrated that, despite being a predominantly T-cell mediated disease, B-cell depletion might still be useful in sarcoidosis patients. In a recent study including 42 patients with sarcoidosis, almost 30% (n=12) of patients showed positive serum titers of antinuclear antibodies when compared with healthy volunteers (81). We recently reported a phase I/II clinical trial (82) of 10 patients with refractory pulmonary sarcoidosis showed improvements in FVC of >5% in one patient and >10% in 4 patients after 24 weeks. 6MWD improved in 5 of 10 patients after 24 weeks. Thus, there were some patients with improvements while others did not benefit. No clear recommendation can therefore be given for the optimal subgroup of patients most likely to benefit from Rituximab treatment.

Importantly, treating physicians not familiar with the use of anti-TNF therapies have to keep in mind that autoimmune reactions to these agents can, albeit rarely, occur. Induction of antinuclear antibodies is common, but clinically apparent systemic lupus erythematosus, demyelinating disorders and also sarcoidosis have been reported (83). Development of anti-drug antibodies can occur which might be prevented by using a combination therapy with low-dose methotrexate or other DMARDs.

Other treatments

Optimal treatment of refractory sarcoidosis not only consists of medical treatment of the disease with second- and third-line agents (see above), but also needs to address complications of fibrotic lung disease, such as infections (e. g. aspergilloma), bronchiectasis and pulmonary hypertension. Physical therapies including pulmonary rehabilitation and physical training programs might improve quality of life and maintain functional parameters despite disease progression (84,85).

Ultimately, lung transplantation has to be considered as an option for the most severely affected patients and early referral to the transplant team should be considered in severely affected patients. As reviewed by Shlobin and Nathan (86), lung transplantation in sarcoidosis patients might be underutilized. Importantly, despite reported recurrences of sarcoidosis post-transplant, mortality is comparable to other conditions (86).

Newer treatment options, namely the anti-fibrotic agent pirfenidone and nintedanib, a multikinase inhibitor, yielded promising results in idiopathic pulmonary fibrosis (IPF) (reviewed in (87)), but have not been investigated in advanced sarcoidosis.

Summary

Sarcoidosis is a heterogeneous disease with variable clinical picture and disease course. Clinical, laboratory and functional evaluation has to be comprehensive in patients not responding to standard therapy and other causes (cardiac dyspnea, pulmonary hypertension, infections) have to be excluded first before patients should be labeled as “treatment-refractory”.

We propose a new definition of refractory disease based on (1) responsiveness to/tolerance of glucocorticoids and (2) progressive pulmonary symptoms despite established therapeutic options.

In refractory cases, disease-modifying anti-sarcoid drugs and biologicals can be used. Methotrexate is preferred by most sarcoidologists, azathioprine and leflunomide are viable alternatives. The different advantages and disadvantages of each agent have to be discussed individually with the patient since none of these medications has been approved for use by the U.S. Food and Drug administration (FDA) or the European Medicines Agency (EMA).

Third-line options include anti-TNF alpha blockers. First choice is Infliximab because of two available double-blind placebo controlled clinical trials, Adalimumab has also been used successfully in many patients with refractory disease. The reason why there are some

agents of the same class (Etanercept and Golimumab) which do not seem to be equally effective, is not convincingly explained until now.

In the future, patients with fibrotic sarcoid lung disease might benefit from newer drugs used in idiopathic pulmonary fibrosis, such as pirfenadine and nintedanib. These agents have not been studied in fibrotic sarcoidosis as of yet.

Lung transplantation is a viable option for the most severely affected patients and should be considered relatively early in the disease course of refractory patients. A multidisciplinary approach is required to identify optimal candidates for transplantation and ultimately approve outcomes.

Equally important in the management of patients with refractory sarcoidosis is the recognition and appropriate treatment of complications, such as infections (aspergilloma, bacterial infections), bronchiectasis, bronchial stenosis and pulmonary hypertension.

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Figure 1. Proposed diagnostic and therapeutic approach to refractory pulmonary sarcoidosis

Abbreviations used: ^{18}F -PET-CT, ^{18}F -positron emission computed chest tomography; 6MW; 6-minute walking test; ADA, adalimumab; AZA, azathioprine; CS, cardiac sarcoidosis; DMASD, disease-modifying anti-sarcoid drugs; INF, infliximab; IV, intravenously; LEF, leflunomide; MTX, methotrexate; PAH, pulmonary arterial hypertension; QoL, quality of life; SQ, subcutaneously.

Level of evidence: A: at least one double-blind placebo-controlled randomized trial with positive results with one or more case series supporting the results; level B: majority of the case series showing positive results; level C: case series with mixed reports of effectiveness or only a small number of case reports. Recommendations are further differentiated into strong (1A, 1B, 1C) or weak (2A, 2B, 2C)

Table 1

Clinical, functional, laboratory and imaging features associated with refractory pulmonary sarcoidosis

Test	Finding	Comments
Clinical findings	Persisting/worsening dyspnea or cough despite treatment Rarely chest pain, wheezing, hemoptysis	Exclude fatigue, infection and pulmonary hypertension as causes of worsening symptoms
Non-invasive tests	Decline of FVC of $\geq$ 5% Lack of improvement of 6MWD	Limited data in sarcoidosis Influenced by multiple factors
Biomarkers	Lack of decline of ACE and/or sIL2-R	Only useful when elevated at baseline Serial measurements necessary
Computed tomography	Lack of improvement / progression from reversible to irreversible findings Potentially reversible findings: Micronodules, nodules, peribronchovascular thickening Irreversible findings: Architectural distortion, bronchial distortion, honeycombing, bullae	Trial of intensified treatment warranted If exclusively fibrosis, assess for complications and treat
^{18}F -PET-CT	Search for sites of active inflammation	Consider more intensified immunosuppressive therapy

Abbreviations used: ^{18}F -PET-CT, ^{18}F -positron emission computed tomography; 6MWD, 6-minute walking distance; ACE, angiotensin-converting enzyme; FVC, forced vital capacity; sIL2-R, soluble interleukin 2-receptor

Table 2

Treatment recommendations for non-steroidal and biological agents

Agent	Starting dose (maximum dose)	Comments	Level of evidence
Disease-modifying anti-sarcoid drugs			
Methotrexate	5–15 mg/week SC/PO (25 mg/week)	Liver and renal insufficiency Use of folic acid (at least 5 mg/week PO) recommended CBC, LFT and Creatinine Risk of hypersensitivity pneumonitis probably <5%	1B
Azathioprine	1 mg/kg/d (two divided doses) PO 2 mg/kg/d	Mutations of TPMT CBC, LFT Co-medication with allopurinol contraindicated	2B
Leflunomide	10–20 mg/d PO	CBC, LFT Lung toxicity reported within first 3 months Silent liver fibrosis	2B
Hydroxychloroquine / Chloroquine	5–7 mg/kg/d PO	Retinopathy (ophthalmologic examination) Cardiomyopathy	2B
Mycophenolate mofetil	500 mg/d PO (2–3 g/d)	CBC, LFT Diarrhea most common adverse effect	2C
Biological agents			
Infliximab	3–5 mg/kg IV week 0,2,6 and every 4–8 weeks thereafter	Tuberculosis screening Infections Autoimmunity Hepatitis reactivation CBC, LFT	1A
Adalimumab	40 mg SC every other week (40 mg SC every week)		2B
Rituximab	1 g IV d 0 and 14	Infections Hepatitis reactivation Test serum immunoglobulins every 3 months Progressive multifocal leukoencephalopathy reported	2B

Abbreviations used: CBC, complete blood count; IV, intravenously; LFT, liver function test; PO, per os; SC, subcutaneously; TPMT, thiopurine methyltransferase

Level of evidence: A: at least one double-blind placebo-controlled randomized trial with positive results with one or more case series supporting the results; level B: majority of the case series showing positive results; level C: case series with mixed reports of effectiveness or only a small number of case reports. Recommendations are further differentiated into strong (1A, 1B, 1C) or weak (2A, 2B, 2C).