New advances in the management of pulmonary sarcoidosis

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ABSTRACT

Sarcoidosis is a highly variable granulomatous multisystem syndrome. It affects individuals in the prime years of life; both the frequency and severity of sarcoidosis are greater in economically disadvantaged populations. The diagnosis, assessment, and management of pulmonary sarcoidosis have evolved as new technologies and therapies have been adopted. Transbronchial needle aspiration guided by endobronchial ultrasound has replaced mediastinoscopy in many centers. Advanced imaging modalities, such as fluorodeoxyglucose positron emission tomography scanning, and the widespread availability of magnetic resonance imaging have led to more sensitive assessment of organ involvement and disease activity. Although several new insights about the pathogenesis of sarcoidosis exist, no new therapies have been specifically developed for use in the disease. The current or proposed use of immunosuppressive medications for sarcoidosis has been extrapolated from other disease states; various novel pathways are currently under investigation as therapeutic targets. Coupled with the growing recognition of corticosteroid toxicities for managing sarcoidosis, the use of corticosteroid sparing anti-sarcoidosis medications is likely to increase. Besides treatment of granulomatous inflammation, recognition and management of the non-granulomatous complications of pulmonary sarcoidosis are needed for optimal outcomes in patients with advanced disease.

Introduction

Sarcoidosis is a multisystem granulomatous syndrome triggered by an unknown agent(s). Sarcoidosis may affect any organ, but it involves the lung in approximately 90% of cases.[1] Clinically significant disease is also common in the skin and eye (20% to 40%).[2] Sarcoidosis has a varied clinical course, ranging from an asymptomatic condition with no significant clinical sequelae to a progressive and/or potentially life threatening condition. The diagnosis of sarcoidosis is often problematic, as there is no clearly accepted diagnostic test or algorithm. Although corticosteroids remain the drug of choice for sarcoidosis, they are commonly associated with side effects that may erode the benefits of the drug. Knowledge concerning sarcoidosis is accelerating exponentially, and numerous innovative drugs and diagnostic tests for sarcoidosis now exist. These developments have led to improved understanding of the phenotypic expression, diagnostic approach, and treatment algorithms concerning sarcoidosis. This article will outline recent advances in the management of pulmonary sarcoidosis. This review is aimed at clinicians caring for patients with sarcoidosis and researchers involved in unraveling the immunopathogenic mechanisms of this disease.

Sources and selection criteria

We performed a PubMed search from January 1980 to 1 January 2019. We included the terms "sarcoidosis" and "treatment" and "therapy." We focused on randomized controlled trials and larger or novel observational studies that investigated treatments for sarcoidosis. We included all randomized controlled trials and selected observational studies that had a substantial impact in the field. We also included important clinical trials from before 1980. We included background as needed to illustrate the discussion.

Epidemiology

The epidemiology of a disease may provide important clues concerning its cause and prevention. A major obstacle to determining the epidemiologic features of sarcoidosis is that the disease has a highly variable clinical presentation. As many as 50% of individuals with sarcoidosis never manifest clinical disease, and up to 30% of them have a spontaneous remission.[3] In addition, the signs and symptoms of sarcoidosis are not specific, and it often takes months to years and visits to multiple physicians before the diagnosis of sarcoidosis is made.[4] For these reasons, a sizeable percentage of sarcoidosis cases may escape detection.

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Radiographic screening studies of sarcoidosis usually yield higher incidence rates than clinical studies by detecting more asymptomatic cases. In one study of more than one million Navy recruits screened by chest radiograph, 49% (65/134) of patients with sarcoidosis detected were asymptomatic,[5] and would have probably been missed if detection relied on clinical parameters. One autopsy study suggested that prevalence rates of sarcoidosis may be 40 times higher than clinical prevalence estimates.[6] Another obstacle to obtaining reliable epidemiologic data on sarcoidosis is that the disease tends to be more severe in certain ethnic groups. This may skew the comparative incidence and prevalence rates of various populations.

Given these caveats, some general statements can be made concerning the epidemiology of sarcoidosis. The disease is more common in black people than white, with an incidence ratio of between 2:1 and 7:1[7-9] and a prevalence ratio of between 3:1 and 5:1.[7] In the US, sarcoidosis incidence and prevalence are lower in Hispanic white people than in white people of non-Hispanic ethnicity, and lower still in people of Asian descent.[8] The incidence and prevalence of sarcoidosis have been found to be greater in women than men in the US at a ratio of near 1.5:1; however, another large epidemiologic study in Europe found no sex difference in disease incidence or prevalence,[10] while a further study found a higher incidence in men than women.[11] Despite the fact that previous reports have suggested that sarcoidosis incidence peaks before age 40,[12 13] even these studies found that this was only true for men, with women demonstrating relatively flat incidence rates between ages 30 and 60. A large epidemiologic study confirmed that men but not women have a higher incidence of sarcoidosis between ages 30 and 49.[11] Furthermore, the average age of diagnosis of sarcoidosis was 50 in that study, while another large epidemiologic analysis found that both the incidence and prevalence of sarcoidosis were significantly higher in those aged 45 to 65 than those under 44.[8] African Americans tend to have prevalence rates that peak in the 30 to 39 year age range, whereas white American have relatively flat incidence rates across adulthood.[12] Although some have proposed that the incidence of sarcoidosis has "shifted" toward an older age over the past half century, we believe that there has not been a demographic shift and there are more plausible explanations for these findings. First, old reports detected cases on a clinical basis that biased selection toward symptomatic cases (eg, black patients over white). Second, careful examination of older reports shows results relatively consistent with modern ones; and third, developments in the electronic age have led to analysis of big data that may lead to more reliable results. Before 2016, studies of sarcoidosis incidence rates were based on an average of 1200 incident cases (range 69 to 5536) and studies of prevalence rates were based on an average of 950 incident cases (range 112 to 3750).[11] In 2016 alone, two epidemiologic sarcoidosis studies were published, with 10 787 and 6831 incidence cases and 16 500 and 29 000 prevalence cases, respectively.[8 11]

The relation between epidemiology and cause of sarcoidosis is unlikely to be straightforward, because no clear cause of sarcoidosis has been identified despite major efforts to do so. It is likely that sarcoidosis develops in genetically susceptible individuals through alteration of the immune system in response to an environmental, occupational, or infectious exposure.[14 15] It is possible therefore that different exposures may cause sarcoidosis in different individuals with different genetic make ups. Table 1 lists potential epidemiologic associations with sarcoidosis. These epidemiological links to the disease are most probably incomplete in that they fail to incorporate genetic influences and do not encompass techniques to identify potential infectious agents that may be additional important exposures. Nonetheless, these epidemiologic associations will need to be explained as part of any unified theory concerning the etiology of sarcoidosis.

In summary, recent "big data" demographic analyses of sarcoidosis cohorts have challenged preconceived notions that sarcoidosis is a disease primarily of young people. The disease appears to have a predilection for those over 45, possibly excepting people of black ethnicity. Numerous epidemiologic associations have been found with sarcoidosis. These associations may yield important insights concerning the immunopathogenesis of the disease when coupled with genetic, proteomic, and/or a systems biology approach.

Advances in diagnosis and prognosis

Serum biomarkers

Various serum biomarkers have been proposed to assess the diagnosis, activity, and prognosis of sarcoidosis.[41] Serum angiotensin converting enzyme (SACE) is the prototypical sarcoidosis biomarker. ACE is produced by the epithelioid cell in the sarcoidosis granuloma,[42] and SACE levels have been proposed as a biomarker that reflects the granuloma burden of the disease.[43] The use of SACE as a diagnostic test for sarcoidosis has been debated for decades. SACE has demonstrated a sensitivity for the diagnosis of sarcoidosis between 41% to 100% in various sarcoidosis cohorts, and has specificity ranging from 83% to 99%.[41] The measurement of SACE is confounded by differences in assays, populations examined, the effects of angiotensin converting enzyme inhibitor drugs[44] and anti-sarcoidosis therapy (which can lower SACE levels), and the status of the patient's inter-individual variation of the genomic insertion/deletion (I/D) polymorphism in the ACE gene, which can also affect SACE levels.[45] The consensus is that SACE has inadequate specificity to be used in isolation as a diagnostic test for sarcoidosis, although an elevated SACE level raises suspicion of the diagnosis. The specificity of SACE for diagnosing sarcoidosis appears to be quite high when the SACE is above twice the upper

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Table 1 | Epidemiologic associations with sarcoidosis

General category	Specific category	Findings	Reference
Space and/or time clustering	Seasonal	Increased risk in spring	16-19
		Increased risk in summer	20
		No seasonal variation	21
		Decreased incidence in fall	22
	Space clustering	Increased prevalence in certain regions of Ireland	23
		Higher risks in the north than south	23
		Increased prevalence near the coastline of South Carolina	24
	Space-time clustering	Diagnosed cases lived within 100 miles	25
Familial aggregation		Increased risk in first and second degree relatives	26
		Increased risk in sibling pairs	27
Occupation	Fire fighters	Increased incidence and/or prevalence	28 29
	US military	Increased risk	9 30
	Using insecticides	Increased risk	31
	Musty odor at work	Increased risk	31
	Building materials	Increased risk	32
	Hardware	Increased risk	32
	Garden supplies	Increased risk	32
	Mobile homes	Increased risk	32
	Industrial organic dusts	Increased risk	32
	Electrical/electronic	Decreased risk	32
	Personal service	Decreased risk	32
	Social and rehabilitation services	Decreased risk	32
	Childcare	Decreased risk	32
	Information clerk	Decreased risk	32
	Metal dust/fumes	Decreased risk Increased risk	32 33
	Photocopier toner exposure	Increased risk	34
	World Trade Center dust exposure	Increased incidence	35
	Working in high humidity	Increased risk	33
	Human-made mineral fibers	Increased risk	36
Environmental exposure	Home central air conditioner	Increased risk	31
	Smoking	Decreased risk	31 37
	Wood stove use	Increased risk	38
	Fireplace use	Increased risk	38
	Non-public water use	Increased risk	38
	Living/working on a farm	Increased risk	38
	Living in forest of arable land	Increased incidence	13
	Living in areas with metal industries	Increased prevalence	10
	Living in agricultural areas	Increased prevalence	10
Physical attributes	Obesity	Increased incidence	37 39
	Increased age at menopause	Decreased incidence	40
	Later age at first full term birth	Decreased incidence	40

limits of normal.[41] SACE may also have a role in the assessment of disease activity, although previously mentioned confounders affect the reliability of serial SACE measurements. Similar to limitations of using SACE as a diagnostic test for sarcoidosis, SACE has inadequate sensitivity and specificity to be used in isolation to assess changes in sarcoidosis activity or to make therapeutic decisions.

Other serum biomarkers include those that reflect CD4+T helper cell activation, such as serum interleukin-2 receptor[46] (sIL-2R) and the chemokines CXCL9, CXCL10, and CXCL11[47 48]; and macrophage activation including chitotriosidase,[49 50] lysozyme,[51] and serum amyloid A (SAA).[52] Of these biomarkers, chitotriosidase and sIL-2R show the most promise as biomarkers for disease activity based on the available data. SAA has a potential role as a diagnostic biomarker and was shown to be fairly specific for the diagnosis of sarcoidosis when stained in granulomatous biopsy specimens of sarcoidosis and non-sarcoidosis granulomatous diseases, as well as being measured in the serum.[52 53]

Genetics and emerging biomarkers

Recent innovations in single nucleotide polymorphism (SNP) technology, RNA sequencing, and pathway analysis have been applied to sarcoidosis and yielded potential diagnostic and prognostic biomarkers.

Because sarcoidosis most probably involves the interaction of an exposure with an immune system under genetic control, it is unlikely that examining genes in isolation will be adequate to unravel the immunopathogenesis of sarcoidosis. Nonetheless, insights may be gained by identifying integral genes. Previous studies have found associations between sarcoidosis and specific genes, including various polymorphisms of HLA class I,[54] HLA class II,[55 56] and interleukin 1-α.[57] Genome-wide association studies (GWAS) have identified several

SNPs associated with sarcoidosis, including ones associated with annexin A11,[58] RAB23 (a member of the RAS oncogene complex),[59] and NOTCH4.[59] An immunochip array containing more than 125 000 SNPs was studied in more than 1700 sarcoidosis patients and 5000 controls and found several chromosome loci associated with sarcoidosis, as well as associations with SNPs of genes peaking in regions of BTNL2, HLA-B, HLA-DB1, and interleukin 23-R.[60] Some of the current limitations of the GWAS approach are that some of the identified SNPs have unclear biological significance (eg, non-coding). Unbiased genome-wide analytic approaches may yield greater understanding of sarcoidosis and other diseases by moving beyond specific biomarkers to enable discovery of mechanisms and therapeutic targets based on systems biology approaches. This is a potentially promising approach that we believe needs to be further explored with sarcoidosis.

Studies of gene expression from sarcoidosis-involved tissues may yield important insights into the immunopathogenesis of sarcoidosis. A comparison of gene expression in normal lungs and lungs affected by sarcoidosis found not only the anticipated finding that T helper-1 (Th1) immune response genes were upregulated in sarcoidosis, but also that genes regulating macrophage derived proteases matrix metallo-protease 12 and ADAM-like decysin-12 were also differentially upregulated.[61] A study of differential gene expression in sarcoidosis skin lesions, normal skin of those sarcoidosis patients, and the skin of normal controls found that skin sarcoidosis lesions showed a strong Th1 profile and expression of interleukin (IL)-23 and IL-23R with limited expression of other Th17 pathway genes. IL-21 and signal transducer and activator of transcription 3 (STAT3) were also upregulated in sarcoidosis tissues.[62]

Because gene expression studies from tissue specimens requires performing a biopsy, gene expression of peripheral blood has been analyzed to determine if it can be used as a surrogate to detect granulomatous inflammation in tissues involved with sarcoidosis. Both an algorithm based classifier conducted by a computer[63] and genome-wide peripheral blood gene expression analysis conducted on peripheral blood mononuclear cells[64] were able to reliably distinguish sarcoidosis patients from healthy controls. These studies and others[62] suggest that gene expression of peripheral blood cells may eventually be useful to diagnose sarcoidosis and to monitor the activity of the disease.

Fibrotic sarcoidosis

Although numerous biomarkers of sarcoidosis related granulomatous inflammation have been examined, little attention has been paid to assessing biomarkers of fibrotic pulmonary sarcoidosis. A common cause of disability and death from sarcoidosis relates to pulmonary involvement,[65-67] and most of these cases are directly or indirectly related to fibrotic lung disease. Sarcoidosis related lung fibrosis may directly lead to end stage lung disease and death.[68-70] In addition, sarcoidosis related lung fibrosis may lead indirectly to death by causing several other potentially lethal pulmonary conditions: pulmonary mycetoma,[71] bronchiectasis,[72 73] and sarcoidosis associated pulmonary hypertension.[74]

Fibrosis in sarcoidosis is thought to be a byproduct of granulomatous inflammation,[75] and this hypothesis is strongly supported radiographically[76] and pathologically[68] by examining biomarkers of granulomatous inflammation.[77] Therefore, effective anti-granulomatous therapy should prevent the development of fibrosis in sarcoidosis. However, less than 20% of sarcoidosis patients develop fibrosis.[2 78] Indiscriminate use of corticosteroids or other anti-granulomatous treatments for pulmonary sarcoidosis may arrest fibrosis in the minority at risk for substantial fibrosis at the cost of causing drug toxicity in most patients. Clearly, an unmet need in the management of pulmonary sarcoidosis is the identification of a biomarker to reliably predict lung fibrosis, so that appropriate anti-granulomatous treatment could be given to those prone to develop fibrosis and could be withheld otherwise. In addition, the development of effective anti-fibrotic drugs for sarcoidosis is likely to be of more value than anti-granulomatous drugs for the treatment of sarcoidosis induced fibrosis.

Although there are no validated biomarkers that reliably identify patients with pulmonary sarcoidosis at risk of developing pulmonary fibrosis, recently SNPs have been identified that are associated with an increased risk of pulmonary fibrosis in patients with sarcoidosis. These SNPs associated with fibrocystic sarcoidosis have occurred within the following genes: GREM1,[79] a gene that encodes gremlin (a secreted glycoprotein and member of the bone morphogenetic proteins), CARD15,[80] and TGF-β3.[81] Note that SNPs associated with pulmonary fibrosis in other lung diseases are not necessarily associated with pulmonary fibrosis in sarcoidosis. For example, although SNP rs35705950, a promoter polymorphism for the mucin 5B gene, has been strongly associated with idiopathic pulmonary fibrosis,[82 83] it was not found to be associated with fibrotic sarcoidosis in a cohort of 180 sarcoidosis patients.[84] Other potential biomarkers that have been associated with progressive and/or fibrotic pulmonary sarcoidosis have included significant lymphopenia of CD4, CD8, and CD19 lymphocytes,[85] upregulation of genes related to the interferon pathway and CXCR9, and downregulation of T cell receptor signaling pathways.[86]

Imaging biomarkers

18-F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a useful tool to identify sites of sarcoidosis activity, and has been used to direct diagnostic biopsies.[87] PET is not a specific diagnostic test for sarcoidosis, as it may be positive when malignancies,[88 89] tuberculosis, other infections,[88] and sarcoidosis-like reactions of malignancy are

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present.[89] Furthermore, PET attenuation cannot reliably distinguish these entities.[88 89] FDG uptake may also be seen in areas of pulmonary fibrosis, possibly owing to neovascularization or non-specific inflammation, and therefore may not be specific for active granulomatous inflammation in fibrotic sarcoidosis.[90]

Clinical data suggest that PET scan findings can be used to determine the benefit of additional anti-sarcoidosis therapy as well as the outcome of corticosteroid withdrawal. One retrospective study reviewed 56 sarcoidosis patients with "severe" disease who were "unresponsive to first and second line treatment" and who then received 26 weeks of infliximab.[91] All had 18-FDG PET scans before initiation of infliximab therapy. A strong correlation was seen between the maximum standardized uptake value (SUVmax) of the PET scan and the change in forced vital capacity over 26 weeks. These data suggest that PET scan findings can reliably predict the outcome of infliximab therapy in such patients. SACE and SIL-2R levels also correlated with various pulmonary function measurements in this cohort. Baseline SUVmax, baseline sIL-2R, and persistent SUV while on anti-sarcoidosis therapy have all been associated with increased likelihood of relapse in various sarcoidosis cohorts.[92 93]

Somatostatin receptor scintigraphy (SRS) has surfaced as a potentially useful scanning technique for sarcoidosis. Somatostatin receptor (SSTR) type 2 is expressed by macrophages and epithelioid cells in sarcoidosis patients.[94 95] SRS identified areas of active sarcoidosis in 174/175 (99.4%) and detected more disease than observed on chest computed tomography (CT).[96] Somatostatin receptor based CT/PET had a concordance of 96% with cardiac nuclear magnetic resonance (CMR) for activity in cardiac sarcoidosis patients, although the latter scanning technique identified more positive cases.[97] 68-Gallium-DOTA-tyrosine-octreotide is a 68-gallium tracer with high affinity for SSTR. In a small controlled study of 20 sarcoidosis patients, 68-gallium-DOTA-tyrosine-octreotide PET/CT scanning was superior to 67-gallium scanning in detecting sites of sarcoidosis activity.[98] Note that all these somatostatin receptor related scanning techniques have not included positive and negative control groups, so that their sensitivity and specificity are currently unknown.

In summary, we do not believe that any specific biomarker can function as a diagnostic test for sarcoidosis in isolation, although information from biomarkers may provide evidence supporting or refuting the diagnosis. In terms of biomarkers of sarcoidosis disease activity, the most useful serum biomarkers are SACE and sIL-2R. Imaging biomarkers appear to be clinically useful to detect active disease in specific organs, especially with PET.

Course of disease and decision to treat

The decision to treat sarcoidosis is based on understanding the natural history and extent of the disease, which are necessary to inform discussion with the patient about strategies for treatment and monitoring. The course of sarcoidosis is variable and there is no reliable prognostic biomarker, therefore it is difficult to predict the disease course in untreated patients. Longitudinal assessment of symptoms, physiologic abnormalities, and other tests are usually necessary to gauge the trajectory of the disease. Prognosis should also be considered in relation to specific but only partially overlapping outcomes: remission, progression, or disability and death. Determining the extent of disease is also problematic, as some forms of sarcoidosis such as cardiac and eye involvement may cause no symptoms initially but may be associated with serious adverse outcomes. Because of these issues, the decision to treat sarcoidosis and the approach to treatment are not easily encapsulated in an algorithm, but better outlined as a series of principles. Moreover, the treatment paradigm for extrapulmonary disease is not identical in all circumstances to that for pulmonary disease. In this section, we focus on considerations pertaining to pulmonary disease only.

Although sarcoidosis is thought to be predominantly a benign condition, recent data would suggest otherwise. Several of the most optimistic projections for spontaneous resolution were derived from populations with asymptomatic disease identified by mass population screening and may no longer be relevant for assessment of sarcoidosis in the present day. A survey of major sarcoidosis centers found that more than 40% of sarcoidosis patients followed for more than five years were still receiving anti-sarcoidosis therapy.[99] Certain populations of sarcoidosis patients have markedly higher risks for poor outcomes, including burdensome symptoms, disability, and death.[100-102] Patients at risk for poor outcomes would ideally be identified early in the disease course, allowing for appropriate longitudinal testing, earlier titration of treatment, and use of less toxic chronic therapy strategies, such as corticosteroid sparing medications.

Prognostic indicators

Age, pulmonary fibrosis, and pulmonary hypertension are the main determinants of poor outcomes in chronic pulmonary sarcoidosis.[103] A staging system using physiology (composite physiologic index >40), extent of pulmonary fibrosis >20% on CT imaging, and main pulmonary artery diameter to ascending aorta diameter ratio >1 incorporates markers of fibrosis and indirect assessment of pulmonary hypertension.[104] The presence of any one of the three prognostic indicators in the staging system conferred a hazard ratio of 5.9 (2.7-10.1) for mortality in a British clinic.[104] However, a gap exists in the identification of patients at risk of poor outcomes early in the course of their disease, before the onset of fibrosis or pulmonary hypertension.

Initiation of therapy

Figure 1 depicts a general schema to guide decision making when starting systemic therapy.

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The goal of therapy should be clearly defined and mutually acceptable to both physician and patient. Clinical experience and several controlled studies suggest that short term treatment of pulmonary sarcoidosis leads to variably large improvements of the chest radiograph, pulmonary function tests, and symptoms during the treatment period.[105-110] After treatment is stopped, the beneficial effects on radiographs and pulmonary function testing appear to wane,[107 108] suggesting that treatment only suppresses inflammation while it is administered.[92]

A popular principle for deciding to initiate therapy is to identify patients who are in danger of poor outcomes (eg, organ function is threatened) or who elect to consider therapy with the goal of improving quality of life.[111] Obviously, the latter indication for therapy requires discussion with the patient about the expected benefits and toxicities of any given treatment.

Effect of corticosteroids

An area of controversy is whether corticosteroid therapy might adversely affect the chances for spontaneous resolution.[112 113] It is possible that use of corticosteroids could promote antigen persistence, leading to T cell exhaustion and chronic inflammation.[114 115] In a cohort of 88 HLA-DRB1*03 negative Swedish patients with acute sarcoidosis, 37% of untreated versus 20% of corticosteroid treated patients resolved their disease by two years.[56] A prospective observational study in Philadelphia found that 74% of patients who were treated with corticosteroids experienced a relapse of their disease after tapering, whereas only 8% of initially untreated patients required treatment during follow-up.[113] Similar findings have been observed in Japan.[116] Randomized controlled trials with adequate follow-up, however, have not generally demonstrated either an adverse or a beneficial effect of treatment on the overall likelihood of remission (table 2).[107 117-120] It is possible, but currently unproven, that therapies targeting putative triggers of sarcoidosis might more clearly improve the likelihood of disease resolution.[121 122]

Data on the effect of corticosteroid therapy on the natural history of sarcoidosis are conflicting. In general, there is no consensus that earlier initiation of corticosteroids in unselected patients results in longer term benefits, including prevention of fibrosis, better lung function, or higher chances of remission. In controlled trials with adequate follow-up, there are some suggestions of better long term outcome when patients were treated regardless of progression.[119 120] All medications used to treat sarcoidosis have important toxicities that need to be considered when deciding to embark on therapy. Therefore, many physicians prefer to follow patients longitudinally before recommending initiation of systemic therapy when there is no evidence of imminent danger.

Treatment options

Once the need for therapy is agreed by patient and physician, the treatment strategy should be formulated based on the patient's needs and preferences informed by the medical knowledge of the treating physician. In the subset of patients with initial treatment indications, 50-82% will require prolonged therapy.[113 123-125] Although initial therapy has a high likelihood of suppressing granulomatous inflammation, prolonged therapy may result in the development of cumulative drug toxicities, such that initial benefit of anti-granulomatous therapy may be outweighed by drug induced comorbidities and other side effects. Treatment schema should therefore

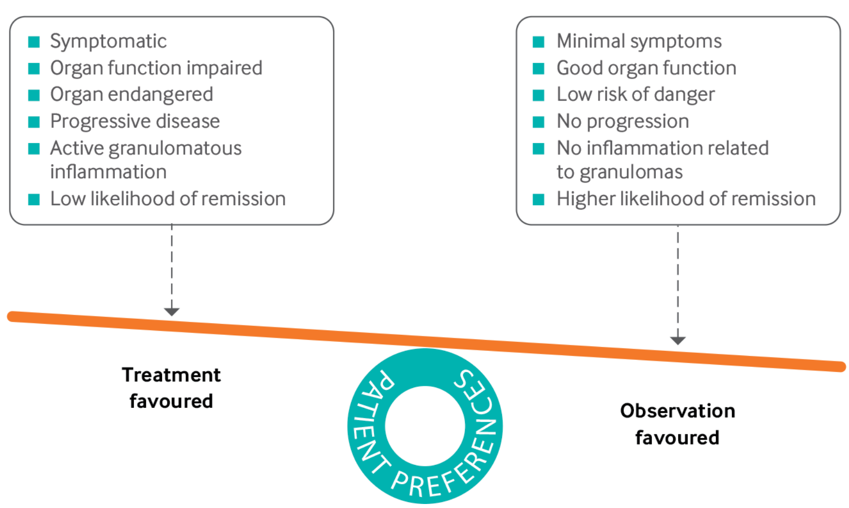

Fig 1 | Assessment of the decision to treat. A therapeutic trial can sometimes be useful to help show whether there is active granulomatous inflammation. Coexisting illnesses (eg, depression, obstructive sleep apnea, obesity) should be sought out and managed. All treatment decisions should revolve around patient input. In patients with higher likelihood of danger but relatively few symptoms, it is crucial to develop a therapeutic relationship with careful explanations about the expectations for therapy, including the side effects and measurable outcomes. Because of the high likelihood of prolonged treatment, steroid sparing therapy should be considered as part of the strategy at the outset or early in the management course

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include considerations about a range of patient and disease specific factors.

Corticosteroids

Corticosteroids have been used for first line management of pulmonary sarcoidosis for more than 60 years, and they remain the most popular systemic therapy.[126 127] Corticosteroids are familiar to clinicians, cheap, quick acting, broadly effective, easily titrated, widely available, and conventionally thought not to require monitoring except for ophthalmologic toxicity screening. For severe extrapulmonary organ threatening sarcoidosis, induction with corticosteroids is typically warranted.[128 129]

For pulmonary disease, the starting dose of corticosteroids and the time required to observe a near maximal response are both less than conventionally suggested. In a retrospective review of 54 treatment naive Dutch patients, the starting dose or cumulative dose of prednisone had no significant bearing on the forced vital capacity or rate of relapse at 3, 6, or 12 months.[130] For acute exacerbations of sarcoidosis, a prednisone dose of 20 mg/day was found to be adequate.[110] The maximal physiologic and symptomatic improvements plateau for most patients within three weeks.[131 132] Finally, relapses of pulmonary sarcoidosis tend to occur at doses below 15 mg/day.[133] For pulmonary sarcoidosis, these observations suggest that a relatively brief initial period of treatment, and a rapid reduction of the daily prednisone dose to less than 15 mg, may improve the balance between treatment effectiveness and toxicity.

The adverse effects of corticosteroids are not always immediately evident,[134] and the chronic sequelae of comorbidities associated with corticosteroid use have not been carefully evaluated. Weight gain is an easily recognized complication that is likely to contribute to other medical problems. In a recent comparison of treated and untreated sarcoidosis patients, initiation of corticosteroids was associated with an adjusted odds ratio of 2.8 (range 1.2-6.3) for a three point increase in body mass index. The risk for excess weight gain continued to accrue even after most patients had stopped corticosteroid therapy.[135] The median weight gain after starting corticosteroids in other sarcoidosis populations ranges from 3.3 kg to 11.7 kg[119 130 136]; weight gain did not tend to reverse in these reports even after corticosteroid tapering.

Epidemiologic data have revealed an unexpectedly high rate of comorbid disease in sarcoidosis populations, including obesity, hypertension, diabetes, hypercholesterolemia, and osteoporosis.[127 137-139] It is not clear whether these associations are a result of sarcoidosis itself, corticosteroid use, or confounding variables. Obesity may be a risk factor for sarcoidosis, rather than a result of sarcoidosis.[139] Nonetheless, data now support the hypothesis that a high proportion of comorbidities in sarcoidosis populations are a consequence of corticosteroid therapy.[135] Taken as a whole, the emerging recognition of the long term risks of corticosteroid therapy should warrant earlier and more aggressive inclusion of corticosteroid sparing medications alongside corticosteroids when treatment is predicted to be prolonged (table 3).

Second line therapy

Methotrexate, azathioprine, leflunomide, and mycophenolate are often viewed as second line therapy for sarcoidosis.[128 140] The term “cytotoxic” is a misnomer, since their mechanism of action is not primarily through induction of leukocyte

Table 2 | Controlled studies with long term follow-up for treatment of pulmonary sarcoidosis

Cohort	Number	Design	Treatment	Population	Stage 1/ stage 2-3 (n/n)	Follow-up	Outcomes	Relapse/long term outcome
Israel[108]	83	Double blind randomized placebo controlled	Prednisone 15 mg daily ×3 months	New diagnosis	37/46	3 months 5.3 years mean	54% prednisone *v* 24% (PLCB) Improved	59% (prednisone red) *v* 47% (PLCB) improved; progression in 38% (prednisone) *v* 16% (placebo)
Selroos[107]	37	Open label random	MP, various doses ×7 months	Persistent <5 years since diagnosis	0/37	7, 24, 48 months	89% (prednisone) *v* 61% (PLCB) improved chest radiograph at 7 months	No chest radiograph, PFT or clinical differences persisted at 48 months
Harkleroad[117]	25	Alternating	Prednisone 60 mg tapering to 20 mg × 6 months	Recent disease and abnormal gas transfer	8/14	≥10 years	No PFT or mortality differences	All 4 patients with normal chest radiograph were untreated
Eule[118]	172	Open label random	Prednisone 40 mg tapering to 10 mg for 6 or 12 months	Asymptomatic	67/105	Minimum 5 years mean 8.9 years	All 3 patients with progression disease in treated group	Relapse 22% in treated, 16% in untreated
Gibson[119]	58	Alternating	Titrated to normalize chest radiograph, for 18 months	Persistent infiltrates after 6 months without progression	0/58	5 years	Mean vital capacity 100% *v* 91% for treated *v* selectively treated; other endpoints no different	6/31 initially untreated patients required steroids during follow-up
Pietinalho[120]	149	Double blind randomized placebo controlled	Prednisolone × 3 months followed by inhaled budesonide × 15 months	Newly diagnosed	79/70	5 years	Forced vita capacity and DLCO both better at 18 months and 5 years in treated group	16/18 relapses were in placebo group

DLCO=diffusing capacity of the lungs for carbon monoxide; PLCB=placebo; PFT=pulmonary function test; MP=methylprednisolone.

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death; rather, these agents work by inhibiting cell activation, proliferation, and migration, through cytokine modulation, or through generation of extracellular anti-inflammatory mediators including adenosine.[141-143] Although these agents have also been called "disease modifying anti-sarcoidosis drugs" (DMASDs),[144] this label is also not precise, since none of them have been shown to alter the natural history of the disease, in contradistinction to the use of DMARDs in rheumatoid arthritis. The term "second line anti-sarcoidosis therapy" best denotes the level of data and the extant clinical approach for this group of agents.

Methotrexate is the most widely studied and commonly prescribed medication among the second line agents.[126] It is the only corticosteroid sparing agent that has been evaluated in a randomized, double blind, placebo controlled trial that included 24 patients, where the drug was shown to be effective for reducing steroids dose and improving symptoms in acute pulmonary sarcoidosis.[136] One case-control study compared the outcomes of pulmonary sarcoidosis in 200 patients in two settings, a Dutch clinic using methotrexate and a Belgian one that relied on azathioprine.[145] Both agents demonstrated similar improvements of pulmonary function tests and corticosteroid reduction, but the frequency of side effects was higher in the group treated with azathioprine.[145] Two retrospective series totaling 108 patients suggested that leflunomide may be more tolerated than methotrexate, and that the combination of both may be more effective than either alone.[146 147] No other controlled data are available to aid in decision making about choice of agents. In practice, patient characteristics, patient preferences, and clinician familiarity with each option are the main factors governing treatment choices.

Among the three agents with the best evidence of effectiveness (methotrexate, leflunomide, and azathioprine),[136 145-149] several patient features are helpful to guide decisions. Methotrexate should generally be avoided in those with renal disease, or liver disease not related to sarcoidosis. Since methotrexate accumulates in extravascular fluid, caution should be exercised in the setting of pleural or peritoneal effusions. Liver toxicity is higher in patients who consume substantial quantities of alcohol.[150] Peripheral neuropathy, a notable side effect of leflunomide, occurs more often in patients who have diabetes or who are older.[151] Considerations regarding alcohol use are similar to methotrexate. Azathioprine carries the least risk of severe hepatic injury, but was associated with more diagnosed infections when compared with methotrexate.[145] Additionally, there is a small but increasingly clear malignancy signal associated with the use of azathioprine, especially in patients over 65.[152 153] Few data are available regarding human fertility and pregnancy; however, azathioprine is probably the safest of the second line anti-sarcoidosis medications for men or women.[154] Leflunomide and mycophenolate should be avoided in men and women who do not use adequate contraception, and methotrexate should also be avoided in pregnancy.[155] Whether methotrexate use in men poses risks for fertility or fetal birth defects is unclear.[156]

Mycophenolate is commonly used to treat interstitial lung disease,[157-159] but the data for sarcoidosis do not suggest much benefit. In a single center retrospective study (n=37), the treatment had no demonstrable effect on pulmonary function trends in patients failing or intolerant of methotrexate and prednisone.[160] A French multicenter review of neurosarcoidosis outcomes in 40 patients suggested higher relapse rates with mycophenolate than with methotrexate, although the treatment strategies were not balanced between the two groups.[161] Despite the paucity of robust evidence, no randomized trial has confidently demonstrated the inferiority of mycophenolate compared with other second line agents.

Tumor necrosis factor antagonists

Monoclonal antibodies that bind tumor necrosis factor (TNF) block cell activation and proliferation, inhibiting granuloma formation and promoting granuloma dissolution.[162 163] Besides blocking TNF signaling, monoclonal TNF antagonists also eliminate TNF-expressing cells through complement dependent cytotoxicity and induction of apoptosis (reverse signaling).[164] Although the soluble TNF receptor construct etanercept is effective for some rheumatic diseases, it is not useful for sarcoidosis.[165 166] The most commonly used agents include infliximab and adalimumab.[167] Golimumab, a human anti-TNF antibody with the advantage of monthly dosing, does not have a large role in contemporary sarcoidosis treatment, possibly because of negative results from a placebo controlled randomized trial.[168] Given the expense of TNF antagonists, biosimilar agents may become increasingly prominent. The effectiveness of one such agent, Inflectra, for sarcoidosis appears to be similar to historically reported responses to infliximab.[169]

Infliximab is a humanized murine IgG antibody that requires intravenous administration. Because of its murine origin, it is more immunogenic than other TNF antagonists, leading to higher rates of

Table 3 | Considerations for choice of anti-sarcoidosis medications

Corticosteroids favored	Steroid minimizing regimens favored
Symptomatic treatment of acute sarcoidosis	Symptomatic organ involvement (pulmonary, ocular, etc), especially when chronic
Rapid disease control needed	Comorbidities (diabetes, obesity, osteopenia, etc)
Brief therapeutic trial when reversibility is unclear	Long term therapy anticipated
Liver or kidney disease limits steroid sparing options	History of poor steroid tolerance
Planned pregnancy	

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anaphylactoid reactions and potentially to the development of anti-chimeric antibodies that cause loss of efficacy, serum sickness, and leukocytoclastic vasculitis. Co-administration of methotrexate, leflunomide, or other immunosuppressants is recommended to decrease the chances of developing anti-chimeric antibodies.[167] A randomized double blind placebo controlled trial in 138 patients showed that infliximab at doses of 3 mg/kg or 5 mg/kg is well tolerated and effective for treatment of pulmonary sarcoidosis.[170] Patients treated with infliximab experienced a mean increase of 2.5% forced vital capacity compared with no change in the placebo treated patients (P=0.04). The benefits were more pronounced in individuals with lower forced vital capacity, more dyspnea, and more chronic disease. The usefulness of infliximab appears to also extend to extrapulmonary disease.[171-173] However, the marginal positive effect of infliximab for patients using prednisone at doses ≥15 mg/day was minimal.[174]

Adalimumab, a fully humanized monoclonal antibody, is also reportedly efficacious for sarcoidosis, but it has not been studied in any randomized controlled trial for pulmonary sarcoidosis. Furthermore, no trials have directly compared the effectiveness of adalimumab with infliximab for pulmonary sarcoidosis. In a small double blind placebo controlled trial (n=16), adalimumab was effective for cutaneous sarcoidosis.[175] For uveitis, including a small number of patients with ophthalmologic sarcoidosis, the two agents appear to be equally useful.[176] Adalimumab is also efficacious for individuals who develop secondary therapy failure during infliximab treatment because of antibody formation or intolerance.[177] Adalimumab is more effective when the dosing strategy is similar to that used for inflammatory bowel disease, with a loading dose and weekly administration.[167]

Antimalarial agents

In general, antimalarial medications have a minor role in the treatment of pulmonary sarcoidosis, but can be complementary. These medications are more widely espoused for the management of disordered metabolism of vitamin D, mild to moderate cutaneous sarcoidosis, and occasionally for other manifestations such as sarcoidosis of the upper respiratory tract. Hydroxychloroquine is used most often owing to its lower toxicity, but chloroquine was the active agent in the only randomized trial of antimalarials in pulmonary sarcoidosis.[178] Chloroquine was shown to decrease the risk of relapses and the rate of pulmonary function decline during prolonged therapy in 18 randomized patients.[178] Nonetheless, the role of antimalarial agents for pulmonary sarcoidosis is mainly limited to adjunctive therapy to augment corticosteroid sparing regimens.

Repository corticotrophin

The US Food and Drug Administration approved adrenocorticotrophin injections for the management of symptomatic pulmonary sarcoidosis in 1952, but this medication was not used for sarcoidosis for several decades after the ascendance of corticosteroids. Repository corticotrophin induces cortisol release through activation of melanocortin receptor 2 in adrenal cells, but the effect of repository corticotrophin is also mediated by four other melanocortin receptors that are widely expressed on immune cells.[179] The relative importance of glucocorticoid receptor (cortisol) activation versus the effects of other melanocortin receptors in pulmonary sarcoidosis is unclear. In a prospective trial of 18 patients with progressive pulmonary sarcoidosis, 24 week treatment with repository corticotrophin was associated with improved DLCO, quality of life, and pulmonary FDG avidity on PET scan, as well as reductions of prednisone dose.[180] At present, use of repository corticotrophin is restricted to the US, and the precise patient population for whom it should be prescribed is not yet clear.

Other agents

Several other medications have either been used historically, or have been described in case reports, but are not widely used. Chlorambucil, an alkylating agent, was used in the past in some centers for refractory disease, generally before widespread adoption of medications like methotrexate and infliximab.[181 182] Thalidomide, which antagonizes TNF and also has anti-angiogenic properties, has been studied, but the pulmonary response is modest, and the therapeutic index is low, with tolerability issues frequently limiting the dose.[183 184] Pentoxifylline is an oral agent that can also inhibit TNF. In an open label trial, 11 of 18 treated patients exhibited a positive response to pentoxifylline, but the benefits of the medication were not re-demonstrated in a randomized placebo controlled trial.[185 186]

Rituximab, an anti-CD 20 monoclonal antibody, depletes B cells. Although humoral immune mechanisms are not conventionally thought to be important in most forms of sarcoidosis, a handful of B lymphocytes can be seen in the sarcoidosis granuloma.[187] Rituximab may also modulate regulatory T cell activity. In a small prospective case series, rituximab resulted in variable improvements in some physiologic markers in a group of patients with refractory pulmonary sarcoidosis.[188] Further controlled studies are needed before rituximab can be incorporated into management algorithms for pulmonary sarcoidosis.

Therapeutic implications of pathogenesis

Other than biologic therapies, the treatment of sarcoidosis has generally relied on medications with broad anti-inflammatory effects. Given the complexity of granuloma immunology and the potential pathogenetic heterogeneity of sarcoidosis, broad based therapies affecting multiple pathways are intrinsically appealing. However, evolving insights about granuloma biology in general, and specifically the pathogenesis of sarcoidosis, are likely to yield

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new therapeutic options. Continued development of acceptable granuloma and/or sarcoidosis models will be important for identification and validation of new therapeutic targets.[189]

The prevailing conceptual model posits that sarcoidosis is a granulomatous reaction to an inciting exogenous agent(s) in genetically susceptible individuals.[190] Evidence for an environmental trigger includes epidemiologic studies that demonstrate case clustering, transmissibility by organ transplantation, and the predominant immune response, typical for that to non-self antigens.[191] Most of the genetic associations conferring risk for sarcoidosis involve the type 2 major histocompatibility complex (MHC II) encoded by genes of the human leukocyte antigen (HLA) region on chromosome 6.[192] Likewise, there is an oligoclonal T cell response, consistent with an immune response to a discrete antigen.[193] Besides an environmental trigger and a genetically driven immune response, it is probable that there are modifier exposures and genes that modulate the risk for development of sarcoidosis and/or its phenotype[194] (fig 2). For example, smoking is a well known modifier exposure that decreases the risk of sarcoidosis, whereas photocopier toner and exposure to certain insecticides both increase risk.[31 34] Modifier exposures might work by directly influencing cell populations (viability, proliferation, macrophage phenotype), transcriptional and translational events, by epigenetic mechanisms, or by structural damage to the lungs.

Causes

The trigger for the sarcoidosis granuloma remains unknown, and in fact there may be more than one exposure capable of inducing sarcoidosis, with variance perhaps largely attributable to geography. A proteomic analysis of sarcoidosis tissues found a mycobacterial virulence factor, mycobacterial catalase G (mKatG), in a high proportion of US patients.[195] Subsequent studies showed the presence of cellular immune responses to multiple mycobacterial virulence factors in sarcoidosis patients but not controls.[196-198] These data led to a single blind controlled study for cutaneous sarcoidosis, and an open label trial for pulmonary sarcoidosis, which both suggested possible efficacy for concomitant levofloxacin, ethambutol, azithromycin, and rifamycin (CLEAR therapy).[121 199] Until a placebo controlled randomized trial shows that treating a trigger of sarcoidosis results in clinically meaningful improvements, use of antimicrobial therapies targeting putative pathogenic triggers is not recommended.

Other investigators have demonstrated similar cellular immune reactions, organismal proteins, and even organismal staining to *Propionibacterium acnes* (*P acnes*) in Japanese sarcoidosis patients.[200-202] In Europe, preliminary evidence shows that fungal antigens may associate with the risk for sarcoidosis, but there are currently inadequate data available to reach a conclusion regarding causality.[203]

Sarcoidosis has not conventionally been considered an autoimmune disease, largely owing to the overwhelming epidemiologic data and the nature of the immune response, a cell mediated type II response dominated by interferon gamma signaling.[191] However, more recent studies have challenged this paradigm. In patients with Löfgren's syndrome, mass spectroscopy and in silico modeling

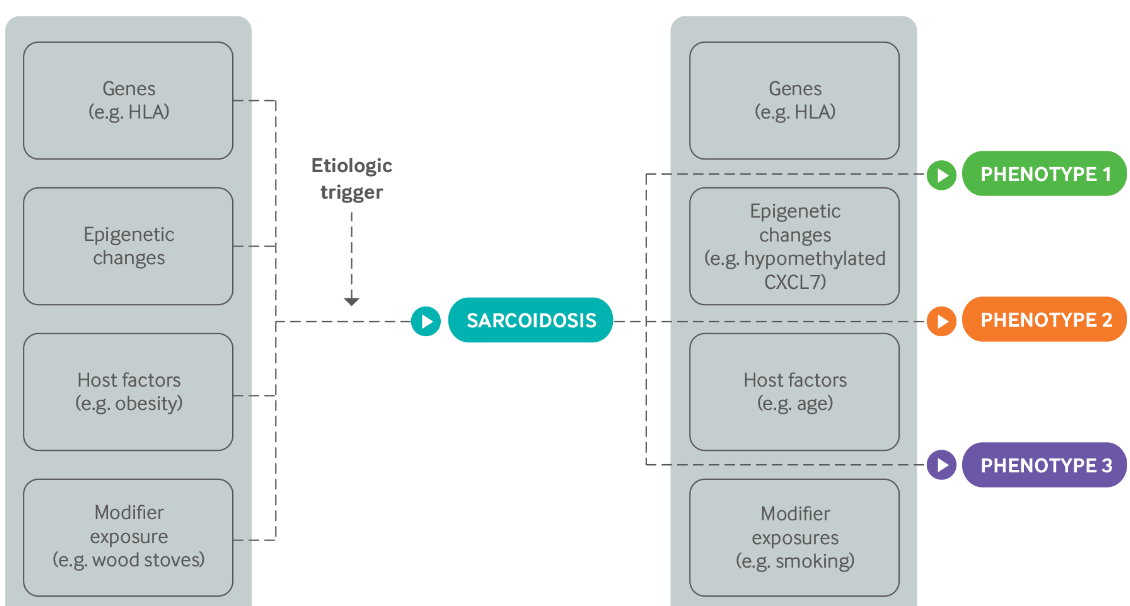

Fig 2 | Interplay between risk factors and the etiologic trigger(s) leads to sarcoidosis. The genetic and non-genetic risk factors, and possibly the etiologic triggers, vary between populations. Once sarcoidosis develops, the outcome and pattern of organ involvement (ie, phenotypes) is also modified by a variety of risk factors, some of which are different from the susceptibility risk factors. HLA=human leukocyte antigen; CXCL7=chemokine (C-X-C) ligand 7

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showed that a self antigen, vimentin, may be the ligand in the MHC and T cell receptor (TCR) trimolecular complex.[204 205] Vimentin staining is present in granulomas from sarcoidosis patients but not controls.[206] Löfgren's patients with HLA-DRB1*03 harbor high concentrations of anti-vimentin IgG and IgA.[207] It is possible that self antigens may become involved through the process of molecular mimicry after an initial exogenous trigger.[208] It is unclear whether autoimmune mechanisms alone are sufficient or even necessary to develop sarcoidosis. Quite possibly, the immune reaction is complex such that autoimmunity functions as a modifier component of a larger immune response.

Another consideration is whether Löfgren's syndrome should be considered a separate disease from other forms of sarcoidosis; ongoing studies will evaluate whether the pathogenic insights derived from Löfgren's syndrome cohorts translate to other forms of sarcoidosis. If autoimmunity is established as an important mechanism in sarcoidosis, other therapies might be deemed attractive, such as agents targeting B cells (eg, rituximab), B cell activating factor (eg, belimumab), or IL-17 (eg, secukinumab).

Genetics

Besides HLA genes, several genetic associations relevant to the immune response have been identified and replicated in sarcoidosis patients within the past decade. Some of these associations are likely to yield therapeutic targets, whereas others may be useful as biomarkers for prognosis and for detecting organ involvement. From a practical perspective, the only genetic association with sufficient validation for widespread clinical adoption is the association of HLA-DRB1*03 positivity with a >90% likelihood of spontaneous disease resolution in Löfgren's syndrome patients.[56] In fact, HLA-DRB1*03 negative patients who were treated with corticosteroids had only a 20% chance for disease resolution at two years. This finding may be interpreted as evidence that treatment of Löfgren's syndrome with this specific HLA genotype decreases the chance of disease resolution, or it may simply imply channeling bias favoring treatment in those with more severe manifestations. Ongoing efforts in relatively large, well phenotyped non-Löfgren's populations are likely to yield additional genetic insights that may facilitate precision therapeutic approaches.

Immunology

The immunologic profile of sarcoidosis is biased toward a Th1 pattern, induced by interferon gamma (IFNg) signaling. Signal transduction activation transduction (STAT1), the canonical target for interferon gamma mediated cell activation, is the central node in the dominant gene expression cassette in sarcoidosis tissues. A wide range of STAT1 dependent cytokines are expressed in sarcoidosis tissues and blood, such as CXCL9, CXCL10, interleukins 2, 12, 15, and 18. Several of these proteins have been associated with progression of sarcoidosis. As such, the JAK-STAT pathway may be a relevant target for future sarcoidosis therapy. In a pilot study, administration of a JAK 1/3 inhibitor, tofacitinib, in a single patient with refractory cutaneous sarcoidosis led to marked improvement of the skin lesions, with accompanying downregulation of IFNg, TNF, mTORC1, and interleukin 6 pathways in biopsy samples.[209]

Although immune responses classically associated with Th1 cells are generally thought to be dominant in the early stages of sarcoidosis, an emerging understanding of T cell biology has demonstrated that there is marked plasticity in T cells. Two groups have demonstrated that most interferon gamma production in sarcoidosis arises from cells with features intermediate between Th1 cells and Th17 cells (Th17.1 cells),[210 211] creating the question of the role of Th17 and associated immune mechanisms in the pathogenesis of sarcoidosis. Whether inhibition of interleukin 17 would be beneficial is unclear. Some data suggest that higher levels of IL-17 are associated with better prognostic sarcoidosis phenotypes[212]; other data have shown that IL17-related mechanisms could have a role in fibrotic lung diseases.[213 214] Regulatory T cell function is impaired in sarcoidosis, with potential pathogenic implications owing to failure to downregulate inflammation or induce tolerance.[215] Although a pilot study of nicotine therapy and a trial of vasoactive intestinal peptide demonstrated the possibility of improving regulatory T cell function with medical therapy,[216 217] it is not yet clear whether clinical outcomes will be improved.

Innate immune mechanisms are a burgeoning area of interest. Serum amyloid A, an acute phase reactant synthesized in the liver, is present in an insoluble form in sarcoidosis granulomas. It may inhibit anti-inflammatory immune mechanisms and augments granuloma formation in animal models.[52] If serum amyloid A has a uniquely pivotal role in sarcoidosis granulomas, its presence may account for certain clinical features of sarcoidosis, such as variable spontaneous resolution and persistence of antigen. Inhibition of serum amyloid A is an attractive therapeutic target that remains untested.

Recent evidence also suggests that granuloma formation is augmented by the mammalian target of rapamycin (mTOR) pathway, in both a murine model and by assessment of gene expression in human sarcoidosis patients.[218 219] The mTOR pathway is a critically central integrator of multiple exogenous and endogenous signals that serves to control cell proliferation and responses[220]; variation in mTOR signaling could partly explain some clinical observations about sarcoidosis risk such as the female preponderance and the higher rate of disease in obese patients.[8 139] It is unlikely that constitutive mTOR activation is sufficient to cause sarcoidosis in the absence of specific antigenic triggers, but more investigation is needed to elucidate this point. Besides mTOR, other innate immune mechanisms, such as intracellular pattern recognition receptors, may also be useful targets for future therapies.[221]

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Fibrosis

Very little is known about the pathobiology of the fibrotic response in sarcoidosis. Gene expression analysis suggests that it is similar to fibrotic chronic hypersensitivity pneumonitis, with important roles for pathways related to immune cell activation and host defense.[222] The current conceptual model holds that the fibrosis in sarcoidosis is a result of attempts to compartmentalize and heal the nidus of ongoing granulomatous inflammation. In support of this hypothesis, pathologic data from sarcoidosis explants demonstrate that the fibrosis is concentrated in the same anatomic distribution as for granulomatous sarcoidosis, and that much of the grossly fibrotic lung consists of concentric hyalinized granulomas with a central core of residual histiocytes.[68 70] Myofibroblasts can be found frequently within and around pulmonary granulomas, including in sarcoidosis.[223] On the other hand, there is no evidence to support a role for epithelial mesenchymal transition as a mechanism in fibrotic sarcoidosis.[224] Since the mechanism of fibrosis is not yet well understood, the possible role of anti-fibrotic medications will require additional study.

Management of difficult clinical issues

Certain manifestations of pulmonary sarcoidosis are problematic to treat and cause significant morbidity and mortality. Sarcoidosis associated pulmonary hypertension is one example. The condition occurs in approximately 6% of sarcoidosis patients,[74] although it is substantially more frequent in patients with more severe disease, with rates of 20-50% in sarcoidosis patients with significant dyspnea [225] or undergoing echocardiography[226 227] and a frequency of up to 79% of sarcoidosis patients listed for lung transplantation[228-230] (table 4). A detailed echocardiographic analysis of a sarcoidosis cohort suggested that occult right ventricular dysfunction is present in several patients without pulmonary hypertension,[231] which might suggest the presence of subclinical myocardial sarcoidosis or a forme fruste of sarcoidosis associated pulmonary hypertension.

Sarcoidosis associated pulmonary hypertension

Sarcoidosis associated pulmonary hypertension is a potentially lethal condition. Mean pulmonary arterial pressure was associated with mortality in an analysis of more than 400 sarcoidosis patients awaiting lung transplantation.[232] In an analysis of 130 patients with sarcoidosis who underwent right heart catheterization for unexplained dyspnea, increased mortality was found in those with a pulmonary hypertension plus a normal pulmonary artery occlusion pressure.[225]

Sarcoidosis associated pulmonary hypertension may develop through several mechanisms. Pulmonary venous hypertension may result from cardiac sarcoidosis, but is more commonly the result of ischemic or hypertensive heart disease from chronic corticosteroid use causing hypertension and/or diabetes.[225] The most common mechanism of sarcoidosis associated pulmonary hypertension is probably related to distortion of the pulmonary vasculature because of parenchymal lung fibrosis.[74 226] Other causes of sarcoidosis associated pulmonary hypertension include granulomatous involvement of the pulmonary vasculature, which is typically more prominent in the pulmonary veins than arteries,[233] parenchymal sarcoidosis causing hypoxic pulmonary vasoconstriction, extrinsic compression of the pulmonary vasculature from adenopathy (rare), and possibly chronic thromboembolic pulmonary hypertension as sarcoidosis patients have been found to be at increased risk of pulmonary embolism.[234]

The approach to screening sarcoidosis patients for pulmonary hypertension has not been standardized. Table 5 lists clinical factors that should raise the suspicion of sarcoidosis associated pulmonary hypertension. Some[240] but not all[128 241] cardiac sarcoidosis experts have recommended that an echocardiogram should be a routine screening test for cardiac sarcoidosis. If such screening for cardiac sarcoidosis were performed, sarcoidosis associated pulmonary hypertension could also possibly be suggested. However, it is important to note that sarcoidosis associated pulmonary hypertension is most common in patients with chronic fibrotic disease that is unlikely to be present at disease presentation. In addition, as with other forms of pulmonary hypertension,[242] although the echocardiographic estimate right ventricular systolic pressure correlates with pulmonary arterial systolic pressure, the sensitivity and specificity of this measurement for sarcoidosis associated pulmonary hypertension is inadequate to reliably confirm or exclude diagnosis.[225] Therefore, the diagnosis needs to be confirmed by right heart catheterization.[225] Echocardiographic measurement of tricuspid annular plane systolic excursion[243] and other echocardiographic parameters[231 244] show promise as diagnostic biomarkers for sarcoidosis associated pulmonary hypertension but await further evaluation.

Although clinical data concerning the treatment of sarcoidosis associated pulmonary hypertension are sparse, pulmonary vasodilators may provide benefit. Case reports and case series have demonstrated a benefit in a subgroup of patients with sarcoidosis associated pulmonary hypertension who have

Table 4 | Frequency of pulmonary hypertension in various cohorts

Cohort	%	No	Method of detection	Ref
Consecutive patients	6	246	Est RVSP ≥40 mm Hg	74
Lung transplant referrals	79	25	RHC mPAP >25 mm Hg	230
Lung transplant waiting list	74	363	RHC mPAP ≥25 mm Hg	229
Persistent dyspnea	54	130	RHC mPAP ≥25 mm Hg	225
PVH	15		PCWP ≤15 mm Hg	
PAH	39		PCWP >15 mm Hg	
Undergoing echocardiography	54	106	Est RVSP ≥40 mm Hg	226
AND Scadding stage IV	70	33	Est RVSP ≥40 mm Hg	
AND no Scadding stage IV	44	34	Est RVSP ≥40 mm Hg	
Undergoing echocardiography	21	96	Est RVSP ≥40 mm Hg	227

RVSP=right ventricular systolic pressure; RHC=right heart catheterization; mPAP=mean pulmonary artery pressure; PVH=pulmonary venous hypertension; PAH=pulmonary arterial hypertension; PCWP=pulmonary capillary wedge pressure.

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received phosphodiesterase inhibitors,[230 243 245] endothelial receptor antagonists,[235 243 245 246] and intravenous and inhaled prostacylins.[247 248] One randomized placebo controlled trial (involving 30 evaluable patients) of bosentan for sarcoidosis associated pulmonary hypertension showed that bosentan but not placebo significantly reduced mean pulmonary arterial pressure and decreased pulmonary vascular resistance.[249] There was no statistically significant change in 6 minute walk distance for either group. A meta-analysis of 28 to 56 patients with sarcoidosis associated pulmonary hypertension (depending on the parameter studied) found that pulmonary vasodilator therapy resulted in a significant mild reduction in mean pulmonary artery pressure (mean 8 mm Hg); a significant increase in cardiac output (mean 0.8 L/min); a statistically significant decrease in pulmonary vascular resistance (mean −4.2 Woods units); and a trend toward an increase in 6 minute walk distance (mean 31, 95% confidence interval −3 to 63).[250] In terms of meaningful clinical outcomes from treatment of sarcoidosis associated pulmonary hypertension, the data are quite limited. A report of 81 patients with the condition treated with pulmonary vasodilator therapy had an improved World Health Organization functional class, but no improvement in 6 minute walk distance or survival.[251] Another report of 33 sarcoidosis associated pulmonary hypertension patients treated with pulmonary vasodilators found that 14 (42%) had an improvement in World Health Organization functional class.[243]

Bronchiectasis

Bronchiectasis is an underappreciated complication of pulmonary sarcoidosis. Bronchiectasis may result from granulomatous airway lesions that have scarred,[252] or from traction bronchiectasis related to parenchymal lung scarring.[72 253] Bronchiectasis has been found in nearly half of patients with fibrocystic sarcoidosis.[72] Bronchiectasis may cause substantial airflow obstruction.[252 254] In patients with fibrocystic sarcoidosis , those with bronchiectasis more commonly have acute worsening episodes (events requiring antibiotics or corticosteroids).[72]

Table 5 | Clinical factors associated with sarcoidosis associated pulmonary hypertension in sarcoidosis patients

Clinical factors	Ref
Dyspnea out of proportion to spirometric decline	226
Fibrocystic sarcoidosis	74 225 226 235 236
Hypoxemia	227
Need for supplemental oxygen	227 229 237
% predicted DLCO significantly reduced	225 229
DLCO <60% predicted	238
% predicted DLCO less than % predicted FVC	225
O_2 desaturation with ambulation/6MWT	227 237
PA diameter increased on chest CT	239
EKG findings suggestive of PH	226
Dyspnea unresponsive to anti-sarcoidosis therapy	225
On lung transplant waiting list	229

DLCO=diffusing lung capacity for carbon monoxide; FVC=forced vital capacity; 6MWT=6 minute walk test; PA=pulmonary artery; CT=computed tomography scan; EKG=electrocardiogram; PH=pulmonary hypertension

Bronchiectasis in fibrocystic sarcoidosis often leads to hemoptysis and pulmonary infection, and it has been recommended that therapy primarily directed at bronchiectasis rather than anti-granulomatous therapy might be most beneficial at this stage.[73]

Aspergilloma

Aspergilloma/mycetoma have been found in 2% to 6% of sarcoidosis patients.[71 255] In pulmonary sarcoidosis patients, aspergillomas occur almost exclusively in those with fibrocystic disease with a frequency of over 10% in this group.[256] Aspergillomas may cause life threatening hemoptysis in sarcoidosis patients,[256] and patients with mycetoma who have underlying sarcoidosis have a higher risk of death than those with underlying tuberculosis cavities.[257] Generally, patients with sarcoidosis and a mycetoma should be considered for some form of treatment for the mycetoma because of their poor outcome. It is possible that the poor outcome of sarcoidosis patients with mycetoma may relate to the use of immunosuppressive anti-sarcoidosis agents that promote fungal growth. Therefore, management of these patients should include reducing immunosuppressive therapy to the lowest possible dose. Although surgical resection of aspergilloma is considered definitive therapy,[258 259] unfortunately most sarcoidosis patients with aspergillomas have inadequate lung function to tolerate surgery.[260] In addition, such surgery is associated with significant morbidity and mortality.[259 261-263] Although bronchial artery embolization is an effective temporizing procedure to control hemoptysis from aspergilloma, revascularization often occurs that may lead to recurrent hemoptysis that is often less responsive to subsequent bronchial artery embolizations.[264-268] Therefore, bronchial artery embolization must be coupled with surgical resection or, alternatively, an additional therapy outlined below.

Azoles are not adequate for the treatment of acute hemoptysis from aspergilloma because effective therapy requires at least six months of treatment and a large percentage of patients fail to have a complete response.[269-274] Transcutaneous instillation of amphotericin B has been shown to effectively control acute hemoptysis from aspergillomas in sarcoidosis patients,[275] although the long term benefit from this procedure is unknown.

In general, we recommend surgical resection be considered for patients who have acute hemoptysis from an aspergilloma who have good pulmonary function (a rare occurrence). Bronchial artery embolization coupled with transcutaneous instillation of an antifungal agent should be considered in patients who are at higher risk of undergoing surgical resection. We recommend a dose of 50 mg of amphotericin B instilled into the cavity by a transcutaneous catheter daily for 10 days.[275] Chronic azole therapy could be considered as suppressive therapy or in patients without an acute episode of hemoptysis. In terms of assessing the response to therapy, resolution of hemoptysis is an

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obvious positive response. In terms of radiographic imaging, reductions in pleural thickness and cavitary wall thickness and complete disappearance of the fungus ball correlate with clinical improvement, whereas mycetoma size and cavitary volume do not.[274]

In summary, most incapacitating and potentially life threatening complications of pulmonary sarcoidosis relate to the development of pulmonary fibrosis. Fibrotic pulmonary sarcoidosis may result in end stage lung disease and respiratory failure, pulmonary hypertension, bronchiectasis with subsequent infection, and the development of a mycetoma. In addition to treating the specific conditions described in this section, an unmet need in sarcoidosis is to develop biomarkers that may detect those with a propensity to develop pulmonary fibrosis and explore potential effective anti-fibrotic treatments.

Guidelines

In 1999, the World Association of Granulomatous Disorders (WASOG), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) jointly published a comprehensive statement on sarcoidosis.[128] A general guideline has not been published since then, but several evidence based guidelines are currently under development with publication expected in 2020: management of sarcoidosis (ERS), diagnosis of sarcoidosis (ATS), diagnosis and management of sarcoidosis-associated pulmonary hypertension (WASOG), and FDG-PET in sarcoidosis (WASOG). Additionally, WASOG has published criteria for the diagnosis of organ involvement from sarcoidosis,[276] and on the use of methotrexate[277] and TNF inhibitors[167] for sarcoidosis.

Conclusion

The diagnosis and management of sarcoidosis has changed considerably over the past decade and will continue to further evolve rapidly over the next decade. As increasingly larger cohorts/populations are studied with unbiased, data driven analytic approaches, novel diagnostic and prognostic biomarkers will be identified. A major challenge is to validate biomarkers across populations, and to demonstrate their utility for management decision making. In parallel, advances in understanding the biology of sarcoidosis and increasing interest in the disease will lead to application of new therapies. Precision medicine approaches, incorporating validated prognostic tools and better predictors (eg, pharmacogenomics) of patient response to treatment may improve outcomes as well as the therapeutic index of anti-sarcoidosis medications. These advances will require collaboration between biologists and sarcoidosis experts to be developed efficiently, and to be clinically relevant. Similarly, patient care for sarcoidosis is increasingly collaborative. Diagnosis and management of the spectrum of pulmonary sarcoidosis manifestations may be optimized by integration of nurses, ancillary staff, and physicians from various specialties, working closely with patients to define individualized approaches to diagnosis and treatment.

RESEARCH QUESTIONS

- What are the genetic, etiologic, and immunologic factors that govern sarcoidosis phenotype and outcome?
- How can the development of progressive disease, and/or fibrosis, be predicted?
- What is the impact of non-corticosteroid therapy on the long term outcome of sarcoidosis?
- What measurable clinical endpoints are best for evaluation of response to therapy?
- What pathogenic targets can be identified for novel therapies?
- What is the overall impact of sarcoidosis and its treatment on morbidity, mortality, and quality of life?

How patients were involved in the creation of this article

Two patients with sarcoidosis reviewed the manuscript and provided useful comments about the content. One is a 59 year old man with primarily cardiac sarcoidosis who had to quit his job as a consequence of his disease. The other is a 46 year old woman with multisystem disease including pulmonary, neurologic, hepatic, splenic, and joint sarcoidosis who developed severe small fiber neuropathy from the disease; she also had to quit her profession after the diagnosis of sarcoidosis. Both patient reviewers provided input that resulted in emphasizing the importance of shared decision making around treatment goals.

Contributorship statement: DAC and MAJ both were involved in the planning of the manuscript, literature review, and writing of the manuscript. Both authors were involved in critical review.

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