Peer reviewed article

Sarcoidosis is a multisystem disorder with variable prognosis – information for treating physicians

Jan A. Wiegand, Martin H. Brutsche

Pneumology, University Hospital Basel, Switzerland

Summary

Sarcoidosis is a chronic granulomatous inflammatory disorder of unknown origin with heterogeneous outcome. In most cases the disease is self-limited, others progress or die from organ involvement, which is often associated with extensive scarring. Although often the primarily affected sites are the lungs and thoracic lymph nodes patients with sarcoidosis must be staged for multi-organ involvement. Modern treatment strategies appraise a critical awareness for the side-effect-ratio of long-term medication. A main interest of research is to identify those patients with unfavourable outcome.

Key words: sarcoidosis; prognosis; gene expression; apoptosis; infliximab; tumour necrosis factor-alpha

Introduction

Sarcoidosis is a chronic multisystem disorder characterised by the presence of non-caseating granulomas and accumulation of T-lymphocytes and macrophages in multiple organs [1]. Up to date the most important enigma of sarcoidosis, ie its aetiology, remains unsolved. The other major challenge of sarcoidosis is its treatment. In some situations it is unclear whether a long-term immunosuppressive treatment should be started or whether one should just wait. Too many patients suffer from treatment-induced morbidity.

Epidemiology

The prevalence of sarcoidosis is estimated at 1–40 per 100 000 inhabitants [1–3]. It is seen throughout the world and affects all races, both sexes and all ages [1, 2]. There are geographical and racial differences in the occurrence of sarcoidosis [1, 4]. In the US sarcoidosis is 3–4 times more frequent in the black ethnicity [3–5]. In European countries sarcoidosis is more prevalent in northern compared to Mediterranean countries [2, 5]. The disease typically affects young adults between 10 to 40 years of age. Familial clustering and case aggregation have been reported [6, 7].

Aetiologic hypotheses

Various theories with arguments for infection, hypersensitivity and autoimmunity exist. In general it is thought that sarcoidosis may result from an exposure to an antigen (infectious agent, aerosols, etc.) in a genetically predisposed, susceptible host [4, 5].

The relationship between sarcoidosis and infectious pathogens is controversial and remains open to further investigation. Spatial, seasonal and occupational clustering is supporting the hypothesis of infective or other exogenous agents. Examples are the outbreaks on the Isle of Man, in northern Sweden or Hokkaido in Japan [6, 8, 9]. In Greece, Spain and Japan most cases are identified in spring and early summer. Certain professional groups appear to be at a higher risk. Clustering has

Financial support:
None

been noted in health care workers, fire fighters and naval aircraft servicemen in the USA [4]. Mycobacteria species, particularly cell wall-deficient forms, were proposed as aetiologic agents. Numerous studies have investigated this hot topic with diverse methodology and conclusions [10–13]. Evidence for a possible role for human herpesvirus 8, and propionibacteria has also been discussed [4, 14].

Genetics

There is a certain familial clustering (approximately 5–19% of cases) suggesting the importance of the genetic background [2]. First- and second-degree relatives of sarcoidosis cases have a significantly elevated risk of sarcoidosis compared with relatives of matched control subjects [15, 16]. Racial and ethnic background also has influence on prevalence and clinical presentation. Black subjects are more likely to have skin involvement other than erythema nodosum, as well as eye, liver, bone marrow and extrathoracic lymph node involvement [1, 16].

Sarcoidosis is a polygenetic disorder. Recent studies were able to demonstrate genetic risk factors (susceptibility genes) for the development of sarcoidosis and identified disease modifying genes associated with specific sarcoidosis phenotypes, like self-remitting stage I sarcoidosis or chronic progressive sarcoidosis. In a genome-wide analysis linkage to a section of the class II major histocompatibility complex (MHC) on the short arm of chromosome 6 was found [17]. Several alleles were associated with susceptibility (HLA DR 2, 11, 12, 14, 15, 17) or protective effects (HLA DR1, DR4 and possibly HLA DQ*0202) for sarcoidosis [4, 17, 18]. Rutherford et al. [18] found HLA-DR2 to be both a susceptibility and poor prognostic marker in sarcoidosis, and DR2-positive patients may particularly benefit from close follow-up and early treatment. In contrast, DR3-positive patients are at a lower risk of chronic disease. Future long-term studies on sarcoidosis probably require stratification for HLA-haplotypes.

Sarcoidosis has a broad spectrum of clinical presentations, which might be the consequence of different pathogenetic mechanisms, maybe even different diseases. Therefore, and to reduce the complexity of genotype/phenotype correlations different studies focussed on the Löfgren's syndrome, which represents a well-characterised homogenous phenotype. HLA DR*0301-DQB1*0201, CCR2 haplotype 2 and female sex were found to be associated with the development of Löfgren's syndrome in one study, but could not be confirmed by Schürmann et al. [19, 20]. Other data suggests that tumour necrosis factor-alpha, lymphotoxin-alpha and HLA-DRB1 gene polymorphisms or a gene located nearby contribute to the susceptibility to sarcoidosis and are associated (directly or via linkage with unknown causative locus) with Löfgren's syndrome [21]. Studies on polymorphisms of the angiotensin-converting enzyme (ACE) are inconclusive [22–25].

The significance and exact genetic locations still remain unclear. Further studies are needed to understand the molecular mechanisms that underlie these associations. The clinical usefulness of genetic tests in patients at risk or with manifest disease has not yet been shown.

Pathogenesis

The past few years have seen remarkable advances in understanding general immunologic and molecular aspects of the mechanisms leading to granuloma formation in sarcoidosis. Accumulation of macrophages and, particularly, CD4-positive T-lymphocytes are present at sites of disease activity, later conglomerating to form granulomata [26, 27]. The process seems to start with presentation of an unknown antigen to T-lymphocytes, via the MHC class II genes. Currently known mechanisms contributing to the cellular accumulation include (1) active migration of CD4-positive T-cells and monocytes from blood under the influence of potent chemotactic factors, including chemokines and respective receptors, MIP-1, MCP-1, RANTES and interleukin (IL)-2, IL-18 [28–35] and (2) *in situ*-proliferation of lymphocytes (IL-2 mediated, [36–39]) and possibly macrophages [40]. Chronic disease has been associated with TNF-alpha, IL-8 and ACE. On the other hand IL-10, IL-12, and IL-18 are said to play a role in disease resolution. However, the mechanism leading to the persistent accumulation of inflammatory cells is not fully understood. Whether or not reduced apoptosis is involved in the pathogenesis of sarcoidosis is unclear [41].

Clinical presentation

The clinical presentation of sarcoidosis is highly variable. The initial presentation is related to sex, race, and age [15, 16, 42, 43]. Thirty to sixty percent of patients remain asymptomatic, and the diagnosis is often an incidental finding [5]. Chronic dry cough, dyspnea and chest pain are the most common symptoms leading to medical attention. Nonspecific constitutional symptoms are frequent and include fatigue, malaise, fever, weight loss, muscle weakness, and exercise intolerance. The combination of fever, erythema nodosum, bihilar lymphadenopathy and polyarthralgias (Löfgren's syndrome) is seen in 20–50% of cases [1, 2, 44–47]. Heerfordt's syndrome (parotid swelling, uveitis, and Bells' palsy) is another specific, but more rare sarcoidosis phenotype.

The pulmonary involvement can vary considerably and the initial radiological staging is a useful prognostic marker. The radiologic staging according to Siltzbach is based on conventional chest X-ray findings (see figure 1) [45]. Clinically relevant extrapulmonary involvement at initial presentation is seen in 7% of patients [1].

In nearly two-thirds of patients spontaneous remission occurs within 2–5 years, whereas chronic or progressive course of disease is observed in 10–30% of patients. Patients with erythema nodosum (eg Löfgren's syndrome) are more likely to have a favourable course of disease [48]. Progressive sarcoidosis can lead to death in approximately 1–5% of cases, mainly due to progressive respiratory insufficiency, central nervous system or heart involvement [1].

Diagnostic criteria

Differential diagnoses

The diagnosis of sarcoidosis is made by exclusion because of a variety of other specific or unspecific granulomatous diseases. Careful history and clinical examination can be helpful in discriminating differential diagnoses from sarcoidosis. The main differential diagnoses include tuberculosis, fungal infections (eg histoplasmosis, coccidiomycosis), other specific infections (e.g. brucellosis, chlamydia, tularaemia), autoimmune disorders (eg Wegener's granulomatosis, Churg-Strauss vasculitis) and malignancies (eg lymphomas, carcinoma). Further important differential diagnoses include chronic beryllium disease, hypersensitivity to other metals/substances (titanium, aluminium, talc, etc.), exogenous-allergic alveolitis and drug-induced pneumonitis (eg methotrexate) [1, 2, 4, 43]. Multiorgan involvement increases the clinical likelihood of sarcoidosis [1]. Clinical presentation and histopathological details are equally important. Typical clinical features include bihilar lymphadenopathy, erythema nodosum, uveitis or other skin lesions (eg maculo-papular lesions, lupus pernio).

The need for biopsy

If sarcoidosis is suspected the diagnosis should be made with a biopsy whenever possible – except for rare cases of typical presentations of a Löfgren' syndrome. The key pathological finding is the non-caseating granuloma. Due to the frequency of pulmonary involvement bronchoscopy is an important diagnostic tool. Bronchoscopy enables the investigator to identify endobronchial lesions, which can be found in almost half of the cases [2, 49, 50]. Simultaneously broncho-alveolar lavage (BAL) can be performed. The diagnostic yield of transbronchial lung biopsies (TBLB) varies from 40–90% and is depending on the stage of the disease and experience of the centre [1, 49, 51, 52]. Most researchers believe 4 to 6 specimens are needed, since sensitivity improves with the number of biopsies. Additional endobronchial biopsy (EBB), transbronchial needle aspiration (TBNA) or endobronchial ultrasound-guided lymph node biopsy (EUNA) can improve the diagnostic yield. Combining TBLB with EBB increases sensitivity by 10–21% [49, 51]. In one study EBB had higher overall diagnostic yield than TBLB [49]. EBB should be performed routinely, but certainly if mucosal abnormalities are present. Frequently patients with sarcoidosis have enlarged mediastinal and hilar lymph nodes. These are potential targets for TBNA or EUNA. With an 18-gauge needle a diagnostic yield of up to 90% can be achieved and add 10–20% to TBLB alone [51]. EUNA can further improve safety and diagnostic yield and will potentially reduce the need for mediastinoscopies in the near future.

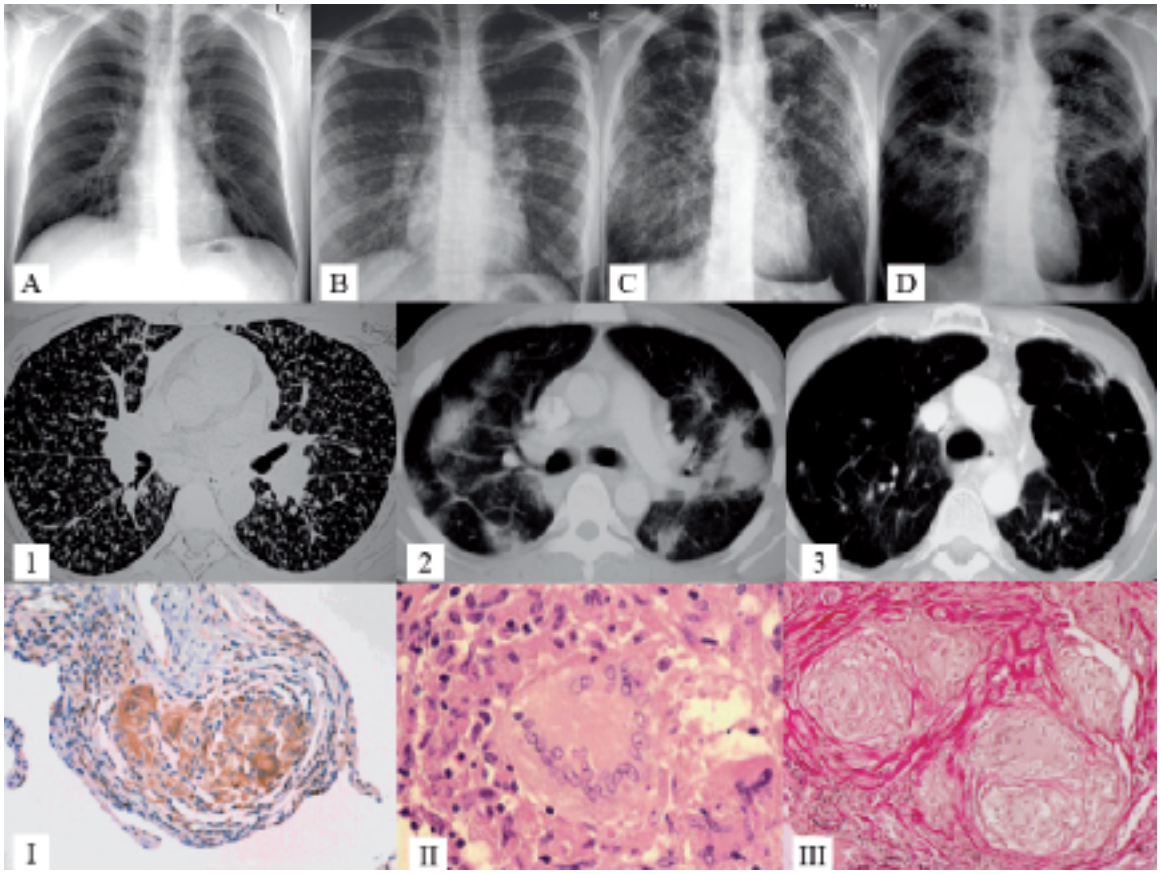
In BAL a lymphocytic alveolitis with a CD4/CD8-ratio >3.5 is highly consistent with sarcoidosis. The sensitivity of CD4/CD8-ratio ranges from 42 to 59% and specificity from 76–96% [53–57]. Welker et al. report a positive predictive value of 69% in a group of patients with suspected interstitial lung disease [58]. BAL fluid lymphocyte counts do not predict disease progression or remission [51].

Imaging

Computed tomography of the chest can help to better characterise the pulmonary abnormalities, but is not a routine diagnostic tool [59–62]. HRCT can be helpful in discriminating inflammatory from fibrotic changes. It may detect parenchymal pathologies in patients with high sus-

Figure 1

Radiological and histological appearances of sarcoidosis. Top row panels A–D show the stages I–IV of the classification of pulmonary sarcoidosis according to Siltzbach [45]. Stage I is defined as bihilar lymphadenopathy (BHL) and is associated with 55–90% complete remission. Stage II consists of BHL and pulmonary infiltrates (40–70% remission). Stage III is characterised by pulmonary infiltrates/interstitial lung disease in the absence of BHL (10–20% remission). Stage IV represents pulmonary fibrosis (0% remission). In the middle row panels specific computed tomography findings are given: panel 1 shows BHL, nodular and reticular interstitial lung involvement and subpleural nodules. Panel 2 demonstrates BHL with parenchymal consolidations of the lungs. Panel 3 represents end-stage lung fibrosis in combination with emphysematous changes. Examples of histological slides are shown in the bottom row: panel I: Histology of a typical non-caseating epitheloid-cell granuloma; panel II: Large magnification of a polynucleated giant (Langerhans) cell; panel III: Dense fibroproliferative scar tissue around epitheloid cell granulomas (Histological slides are kindly provided from Prof. L. Bubendorf).



picion of disease but normal chest x-ray. In patients with sarcoidosis HRCT has a yield of up to 92% of parenchymal findings [63]. Typical CT-findings are symmetric mediastinal and bihilar lymphadenopathy, upper lobe predominance, peribroncho-vascular accentuation and subpleural micronodules (figure 1). Patients with predominantly ground-glass opacity and consolidation patterns on HRCT seem to have a worse prognosis than patients with predominantly nodular patterns and can develop honeycombing [64]. Magnetic resonance imaging (MRI) can help to diagnose brain, muscular-skeletal and heart involvement [4]. Nowadays, gallium scintigraphy is of limited value and should not be used routinely. Positron emission tomography (PET) is probably more sensitive and could help to identify ideal biopsy sites in special cases [65, 66].

Blood tests

There are no specific or diagnostically useful blood tests for sarcoidosis. Most frequent findings include mild anaemia and lymphopenia [67]. Elevated ACE levels are found in 50–75% of cases. Thus, the sensitivity is rather low. ACE can be used as a follow-up tool in patients with elevated ACE-levels [68]. However, the usefulness of ACE is very controversial [69].

Staging for extrapulmonary sarcoidosis

Sarcoidosis can affect virtually all organs. Therefore, all patients with this disease should be staged for extrapulmonary organ manifestation.

Up to 90% of patients have lung involvement. In approximately 30% of patients extrapulmonary manifestations are found during the course of the disease. Organs frequently affected are peripheral lymph nodes, skin (approximately 25% of the cases), heart (5–10%), ocular involvement (25%), central nervous system (5%) and kidneys (rare).

Liver biopsies show granulomatous changes in 40–70% of the cases, but relevant hepatic dysfunction is rare [1, 2]. There are reports of an overlap with chronic inflammatory bowel diseases [16, 70, 71].

The clinical evaluation of patients with proven sarcoidosis should at least include thorough history (including occupational and environmental exposure), physical examination (emphasis on lung, skin, eye, liver, heart), chest radiography, pulmonary function tests (spirometry and diffusion capacity for carbonmonoxide), blood count and chemistry (including calcium, liver enzymes, creatinine and urea), urine analysis (24h-calcium secretion), ophthalmologic examination and an electrocardiogram.

Treatment

The unpredictable course of sarcoidosis – some patients showing spontaneous resolutions while others progress to chronic lung disease (ie fibrosis) – makes treatment decisions challenging. For many patients the most satisfying treatment is no treatment at all. The most important treatment options for sarcoidosis are summarised in table 1.

Corticosteroids remain the cornerstone of treatment. Oral and inhaled corticosteroids are widely used. In principle, only patients with severely active and/or progressive disease qualify for sytemic treatment. However, there is no consensus about when and in whom therapy should be started or about dosage and duration. Some centres treat up to two thirds of their patients [72]. A recent Cochrane review [73] concludes that oral corticosteroids improved the chest radiograph, symptoms and spirometry over 3–24 months. But there is little evidence of an improvement in lung function or sustaining a long-term effect. Patients with stage II or III disease with moderate to severe or progressive symptoms or changes on chest radiograph may have a benefit by oral corticosteroids. Patients with chronic active disease lasting longer than 2–5 years often need long-term therapy. The role for inhalative corticosteroids for patients with pulmonary sarcoidosis is not clearly established, and they do not seem to have a steroid-sparing effect. However, some trials show a benefit on clinical symptoms and lung function [1, 4].

Generally accepted indications and modalities for systemic immunosuppressive treatment are given in figure 2. If fatigue is incapacitating systemic therapy should also be considered. Dosage should be adapted according to clinical and symptomatic response. Usual dosage of steroids vary between 4–40 mg prednisone daily [73]. After an initial induction period, steroid dosage should then be reduced to the lowest possible maintenance level. Duration of therapy depends on indication and response.

Corticosteroid-sparing strategies with other immunosuppressive/immunomodulating agents are only partially successful, and sometimes associated with side effects (ie increased rate of infections). In case of skin lesions or involvement of anterior parts of the eye topical applications are the treatments of choice.

Due to the aetiologic coherence in granuloma formation and the association between high levels of TNF-alpha in BAL with chronic disease, a new strategy to interfere with the TNF-alpha pathway has been developed lately. Few recent reports have shown potential and in some cases respectable ben-

Table 1

Current pharmacological treatment options for sarcoidosis (adapted from Baughman et al. 2003) [4].

Substance (Mechanims)	Proposed use in sarcoidosis	Side effects
Corticosteroids: Prednisone, Prednisolone (IL-2 & TNF-α ↓)	Best studied drug; used for all forms of sarcoidosis; topical application ie skin, inhalation;	Osteoporosis, diabetes, hypertension, insomnia
Chloroquine, Hydroxychloroquine	Skin disease, neurosarcoidosis and hypercalcaemia; steroid-sparing in chronic pulmonary sarcoidosis	Ocular toxicity, nausea
Methotrexate (IL-2 release & TNF-α ↓)	Acute and chronic sarcoidosis; effect delayed (6 months); steroid-sparing	Nausea, neutropenia, hepatoxicity, pulmonary fibrosis
Azathioprine (IL-2 release & TNF-α ↓)	Few data for chronic sarcoidosis; steroid-sparing	Nausea, neutropenia
Pentoxifylline (Lymphocytes & TNF-α ↓)	Efficacy for acute (mild-moderate) disease	Gastrointestinal intolerance (common)
Thalidomide (IL-12 release & TNF-α ↓)	Useful for chronic skin disease; no effect on pulmonary disease, anti-angiogenic	Somnolence, teratogenic, constipation, peripheral neuropathy
Cyclophosphamide	Because of toxicity only for refractory cases	Neutropenia, nausea, cystitis, carcinogenic
Cyclosporine (IL-2 release & T-cell activation ↓)	Possible effect for neurosarcoidosis; no clinical improvement; no steroid-sparing effect	Renal failure, hypertension, can cause lymphoma
TNF-alpha antagonists: Infliximab (monoclonal antibody against TNF-alpha) (Etanercept)	Limited data about effectiveness and dosage; possible use for refractory disease No good evidence for effect	Increased rate of tuberculosis, allergic reaction, possibly carcinogenic

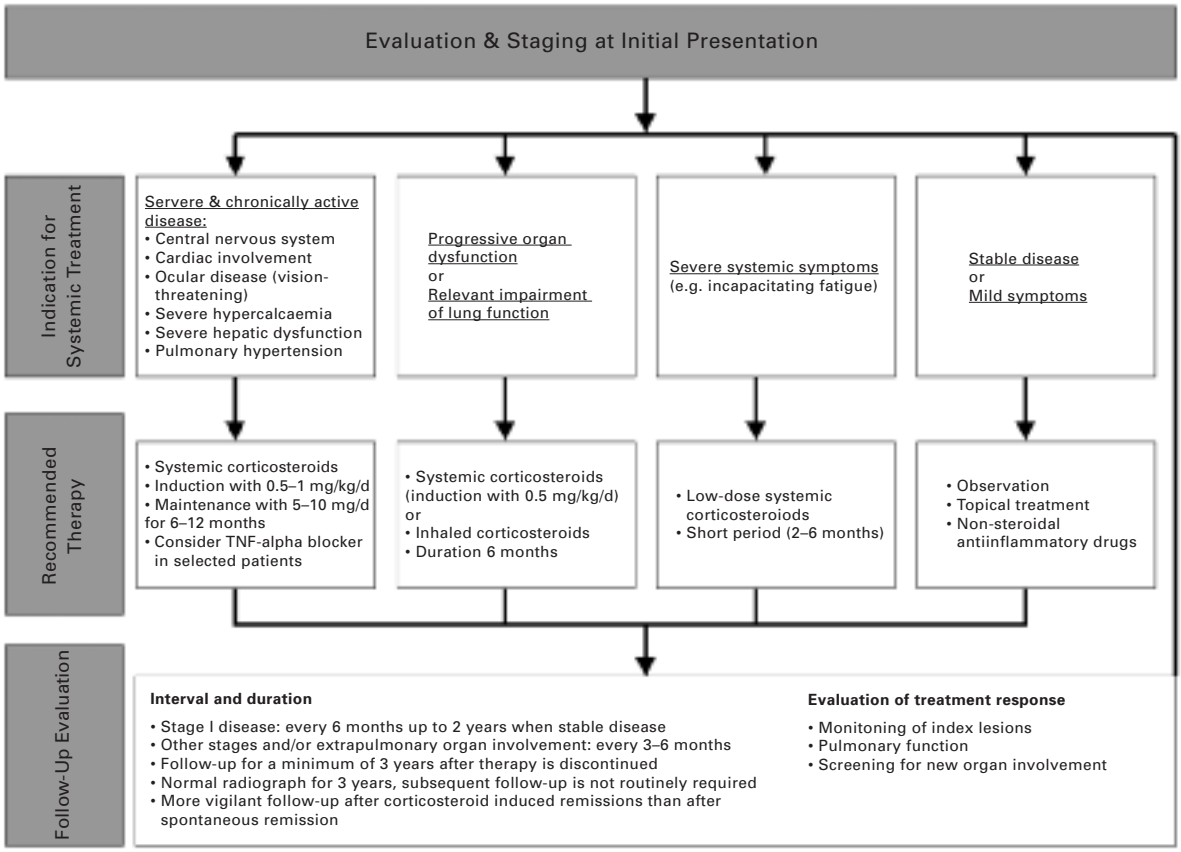


Figure 2

Therapeutic approach of a patient with sarcoidosis (adapted from Thomas and Hunninghake 2003 [5] and Costabel 2001 [61]). In general, only patients with severely active and/or progressive disease should receive systemic treatment.

efit of a specific inhibition of TNF-alpha with the monoclonal antibodies infliximab [74–76]. However, this is with an increased risk of reactivating tuberculosis and other infections, and respective safety measures need to be taken. We recommend the administration only at experiencedcentres. Etanercept, another TNF-alpha-blocker has been proven less effective except for some case reports [77–79]. Clinical studies on the effect of TNF-alpha blocking agents are currently underway. The role of TNF-alpha blockers remains to be established.

Prophylaxis of osteoporosis in sarcoidosis is difficult and controversial. If long-term immunosuppression is planned, oral biphosphonates should be considered. Calcium and vitamin-D supplementation is not without risk as sarcoidosis itself can lead to hypercalcaemia [1].

Sarcoidosis research

Despite intensive research the aetiology and the markers of unfavourable clinical course in sarcoidosis remain challengingissues. Large epidemiological trials helped to improve staging and risk assessment for patients. Among other findings the ACCESS study revealed that women were more likely to have eye and neurologic involvement and erythema nodosum, whereas men were more likely to be hypercalcaemic [15, 16]. In the future new diagnostic markers like CD103/CD4 ratios in BAL might improve non-invasive diagnosis [80].

Studies on the pathogenesis of granuloma formation investigated different inflammatory response pathways. A region of interest is the c-c chemokine receptors. An association between specific CCR5 haplotype (HHC) and persistent lung involvement in sarcoidosis was reported [81]. T-lymphocytes co-expressing CXCR3 and CXCR6 seem to act coordinately with respective ligands and Th1-type inflammatory cytokines in the alveolitic/granuloma phases of the disease [82].

Genome-wide linkage analyses underline the importance of the MHC region to confer a genetic risk for sarcoidosis [17, 83]. Currently, an association with susceptibility to sarcoidosis is investigated for the BTNL2 gene, which resides in the class II MHC region of chromosome 6p and is probably involved in co-stimulation of T-lymphocytes [17, 83, 84]. Many groups are currently searching to understand the exact molecular mechanisms and genetic locations that underlie these associations.

In order to find prognostic markers and potential therapeutic targets new technologies are applied. Gene expression arrays are able to measure many thousands of genes at once. A recent study [41] found that mechanisms controlling apoptosis are playing a key role in the pathogenesis of sarcoidosis. Significant differences in the expression of apoptosis-related genes were found in peripheral blood of patients with acute onset sarcoidosis [18, 41, 85]. Using a target gene approach strategy

early growth response-1 (EGR-1), an immediate early gene, was found to be associated with chronic fibroproliferative lung involvement. EGR-1 was found over-expressed in lung biopsies of sarcoidosis patients. When blocking EGR-1 in an *in vitro*-model of primary human lung fibroblasts, the proliferation of these cells was significantly abrogated [86].

The patients' perspectives

Sarcoidosis often hits young adolescent patients, who just finished their professional education, and are about to found a family. They find themselves in a situation, where it is unclear whether they suffer from a progressively invalidating or a "flue-like" disease. This relevant incertitude – potentially triggered by other mechanisms – leads to a relevant proportion of patients with depression [87, 88]. An open-minded discussion about the impact of the disease on the daily life and mood is very important, and not rarely a psychotherapy with or without the application of an antidepressant medication is indicated.

Another concern of patients with sarcoidosis is that their family physicians or even lung specialist often have little experience with this rare disease or misinterpret their symptoms, which delays diagnosis in many cases. It would often be easier for them to directly see a specialist for sarcoidosis [89]. Patients often seek for alternative treatment approaches with varying response. So far there is no respective evidence.

Future directions

As long as the aetiology of sarcoidosis is unclear, there are no effective prevention strategies. Better and more gene-based prognostic criteria are needed in order to identify individuals, who require are closer follow-up and/or immunosuppressive treatment. Novel pharmacological agents that are more specific than corticosteroids to block inflammation, granuloma formation, and organ scarring, are urgently needed.

Correspondence:
Martin H. Brutsche, MD, PhD
University Hospital
Petersgraben 4
CH-4031 Basel
E-Mail: mbrutsche@uhbs.ch

References

1 Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999;160:736–55.
2 Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med 1997;336:1224–34.
3 Rybicki BA, et al. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol 1997;145:234–41.
4 Baughman RP, Lower EE, du Bois RM. Sarcoidosis. Lancet 2003;361:1111–8.
5 Thomas KW, Hunninghake GW. Sarcoidosis. JAMA 2003; 289:3300–3.
6 Hiraga Y. An epidemiological study of clustering of sarcoidosis cases. Nippon Rinsho 1994;52:1438–42.
7 Pietinalho A, et al. Familial sarcoidosis in Finland and Hokkaido, Japan – a comparative study. Respir Med 1999;93: 408–12.
8 Hills SE, Parkes SA, Baker SB. Epidemiology of sarcoidosis in the Isle of Man – 2: Evidence for space-time clustering. Thorax 1987;42:427–30.
9 Parkes SA, et al. Epidemiology of sarcoidosis in the Isle of Man – 1: A case controlled study. Thorax 1987;42:420–6.
10 Brown ST, et al. Recovery of cell wall-deficient organisms from blood does not distinguish between patients with sarcoidosis and control subjects. Chest 2003;123:413–7.
11 Almenoff P, et al. Growth of acid fast L forms from the blood of patients with sarcoidosis. Thorax 1996;51:530–3.
12 Ang SC, Moscovic EA. Cross-reactive and species specific Mycobacterium tuberculosis antigens in the immunoprofile of Schaumann bodies: a major clue to the etiology of sarcoidosis. Histol Histopathol 1996;11:125–34.
13 Alavi HA, Moscovic EA. Immunolocalization of cell-wall-deficient forms of Mycobacterium tuberculosis complex in sarcoidosis and in sinus histiocytosis of lymph nodes draining carcinoma. Histol Histopathol 1996;11:683–94.
14 Jones RE, Chatham WW. Update on sarcoidosis. Curr Opin Rheumatol 1999;11:83–7.
15 Rybicki BA, et al. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). Am J Respir Crit Care Med 2001;164:2085–91.
16 Baughman RP, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164:1885–9.
17 Schurmann M, et al. Familial sarcoidosis is linked to the major histocompatibility complex region. Am J Respir Crit Care Med 2000;162:861–4.
18 Rutherford RM, et al. HLA-DR2 predicts susceptibility and disease chronicity in Irish sarcoidosis patients. Sarcoidosis Vasc Diffuse Lung Dis 2004;21:191–8.
19 Spagnolo P, et al. C-C chemokine receptor 2 and sarcoidosis: association with Lofgren's syndrome. Am J Respir Crit Care Med 2003;168:1162–6.
20 Valentonyte R, et al. Study of C-C chemokine receptor 2 alleles in sarcoidosis, with emphasis on family-based analysis. Am J Respir Crit Care Med 2005;171:1136–41.

21 Mrazek F, et al. Association of tumour necrosis factor-alpha, lymphotoxin-alpha and HLA-DRB1 gene polymorphisms with Lofgren's syndrome in Czech patients with sarcoidosis. Tissue Antigens 2005;65:163–71.
22 Arbustini E, et al. Polymorphism of angiotensin-converting enzyme gene in sarcoidosis. Am J Respir Crit Care Med 1996; 153:851–4.
23 Maliarik MJ, et al. Angiotensin-converting enzyme gene polymorphism and risk of sarcoidosis. Am J Respir Crit Care Med 1998;158:1566–70.
24 Tomita H, et al. Polymorphism in the angiotensin-converting enzyme (ACE) gene and sarcoidosis. Am J Respir Crit Care Med 1997;156:255–9.
25 Rybicki BA, et al. Sarcoidosis and granuloma genes: a family-based study in African-Americans. Eur Respir J 2004;24:251–7.
26 Hunninghake GW, et al. Characterization of the inflammatory and immune effector cells in the lung parenchyma of patients with interstitial lung disease. Am Rev Respir Dis 1981;123: 407–12.
27 Hunninghake GW, Crystal RG. Pulmonary sarcoidosis: a disorder mediated by excess helper T-lymphocyte activity at sites of disease activity. N Engl J Med 1981;305:429–34.
28 Shigehara K, et al. IL-12 and IL-18 are increased and stimulate IFN-gamma production in sarcoid lungs. J Immunol 2001;166: 642–9.
29 Standiford TJ, et al. Macrophage inflammatory protein-1 alpha expression in interstitial lung disease. J Immunol 1993;151: 2852–63.
30 Ziegenhagen MW, Muller-Quernheim J. The cytokine network in sarcoidosis and its clinical relevance. J Intern Med 2003;253: 18–30.
31 Car BD, et al. Elevated IL-8 and MCP-1 in the bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis and pulmonary sarcoidosis. Am J Respir Crit Care Med 1994; 149:655–9.
32 Girgis RE, et al. Cytokines in the bronchoalveolar lavage fluid of patients with active pulmonary sarcoidosis. Am J Respir Crit Care Med 1995;152:71–5.
33 Ziegenhagen MW, et al. Increased expression of proinflammatory chemokines in bronchoalveolar lavage cells of patients with progressing idiopathic pulmonary fibrosis and sarcoidosis. J Investig Med 1998;46:223–31.
34 Iida K, et al. Analysis of T cell subsets and beta chemokines in patients with pulmonary sarcoidosis. Thorax 1997;52:431–7.
35 Kodama N, et al. Expression of RANTES by bronchoalveolar lavage cells in nonsmoking patients with interstitial lung diseases. Am J Respir Cell Mol Biol 1998;18:526–31.
36 Pinkston P, Bitterman PB, Crystal RG. Spontaneous release of interleukin-2 by lung T lymphocytes in active pulmonary sarcoidosis. N Engl J Med 1983;308:793–800.
37 Hunninghake GW, et al. Role of interleukin-2 release by lung T-cells in active pulmonary sarcoidosis. Am Rev Respir Dis 1983;128:634–8.
38 Semenzato G, et al. Immunohistological study in sarcoidosis: evaluation at different sites of disease activity. Clin Immunol Immunopathol 1984;30:29–40.
39 Muller-Quernheim J, et al. Interleukin-2 receptor gene expression by bronchoalveolar lavage lymphocytes in pulmonary sarcoidosis. Am Rev Respir Dis 1989;140:82–8.
40 Agostini C, et al. Phenotypical and functional analysis of natural killer cells in sarcoidosis. Clin Immunol Immunopathol 1985;37:262–75.
41 Rutherford RM, et al. Functional genomics in sarcoidosis – reduced or increased apoptosis? Swiss Med Wkly 2001;131: 459–70.
42 Rabin DL, et al. Sarcoidosis: social predictors of severity at presentation. Eur Respir J 2004;24:601–8.
43 Newman LS, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. Am J Respir Crit Care Med 2004;170:1324–30.
44 Daweritz C, Brutsche M. Young man with exercise-induced dyspnea. Schweiz Rundsch Med Prax 2001;90:1783–5.
45 Siltzbach LE. Sarcoidosis: clinical features and management. Med Clin North Am 1967;51:483–502.
46 Loddenkemper R, et al. Clinical findings in 715 patients with newly detected pulmonary sarcoidosis – results of a cooperative study in former West Germany and Switzerland. WATL Study Group. Wissenschaftliche Arbeitsgemeinschaft für die Therapie von Lungenkrankheiten. Sarcoidosis Vasc Diffuse Lung Dis 1998;15:178–82.
47 Pietinalho A, et al. The mode of presentation of sarcoidosis in Finland and Hokkaido, Japan. A comparative analysis of 571 Finnish and 686 Japanese patients. Sarcoidosis Vasc Diffuse Lung Dis 1996;13:159–66.
48 Judson MA, et al. Two year prognosis of sarcoidosis: the ACCESS experience. Sarcoidosis Vasc Diffuse Lung Dis 2003;20: 204–11.
49 Shorr AF, Torrington KG, Hnatiuk OW. Endobronchial biopsy for sarcoidosis: a prospective study. Chest 2001;120:109–14.
50 Shorr AF, Torrington KG, Hnatiuk OW. Endobronchial involvement and airway hyperreactivity in patients wih sarcoidosis. Chest 2001;120:881–6.
51 Chapman JT, Mehta AC. Bronchoscopy in sarcoidosis: diagnostic and therapeutic interventions. Curr Opin Pulm Med 2003;9: 402–7.
52 Koerner SK, et al. Transbronchinal lung biopsy for the diagnosis of sarcoidosis. N Engl J Med 1975;293:268–70.
53 Costabel U. Sensitivity and Specificity of BAL findings in sarcoidosis. Sarcoidosis 1992;9(Suppl. 1):211–4.
54 Costabel U. CD4/CD8 ratios in bronchoalveolar lavage fluid: of value for diagnosing sarcoidosis? Eur Respir J 1997;10: 2699–700.
55 Marruchella A, Tondini M. Reliability of bronchoalveolar lavage in the routine clinical assessment of patients with sarcoidosis. A retrospective analysis. Panminerva Med 2002;44: 257–60.
56 Ziegenhagen MW, et al. Bronchoalveolar and serological parameters reflecting the severity of sarcoidosis. Eur Respir J 2003;21:407–13.
57 Greco S, et al. Predictive value of BAL cellular analysis in differentiating pulmonary tuberculosis and sarcoidosis. Eur Respir J 2005;26:360–2.
58 Welker L, et al. Predictive value of BAL cell differentials in the diagnosis of interstitial lung diseases. Eur Respir J 2004;24: 1000–6.
59 Mana J, et al. Excessive thoracic computed tomographic scanning in sarcoidosis. Thorax 1995;50:1264–6.
60 Lynch JP, 3rd, Computed tomographic scanning in sarcoidosis. Semin Respir Crit Care Med 2003;24:393–418.
61 Costabel U. Sarcoidosis: clinical update. Eur Respir J Suppl 2001;32:56s–68s.
62 Drent M, et al. Sarcoidosis: assessment of disease severity using HRCT. Eur Radiol 2003;13:2462–71.
63 Halme M, Piilonen A, Taskinen E. Comparison of endobronchial and transbronchial biopsies with high-resolution CT (HRCIT) in the diagnosis of sarcoidosis. Apmis 2001;109: 289–94.
64 Akira M, et al. Long-term Follow-up CT Scan Evaluation in Patients With Pulmonary Sarcoidosis. Chest 2005;127:185–91.
65 Mana J. Nuclear imaging. 67Gallium, 201thallium, 18F-labeled fluoro-2-deoxy-D-glucose positron emission tomography. Clin Chest Med 1997;18:799–811.
66 El-Haddad G, et al. Evolving role of positron emission tomography in the management of patients with inflammatory and other benign disorders. Semin Nucl Med 2004;34:313–29.
67 Lower EE, et al. The anemia of sarcoidosis. Sarcoidosis 1988;5: 51–5.
68 Studdy PR, Bird R. Serum angiotensin converting enzyme in sarcoidosis – its value in present clinical practice. Ann Clin Biochem 1989;26:13–8.
69 Shorr AF, Torrington KG, Parker JM. Serum angiotensin converting enzyme does not correlate with radiographic stage at initial diagnosis of sarcoidosis. Respir Med 1997;91:399–401.
70 Rutherford RM, et al. Prevalence of coeliac disease in patients with sarcoidosis. Eur J Gastroenterol Hepatol 2004;16:911–5.
71 Judson MA, et al. The diagnostic pathway to sarcoidosis. Chest 2003;123:406–12.
72 Hunninghake GW, et al. Outcome of the treatment for sarcoidosis. Am J Respir Crit Care Med 1994;149:893–8.
73 Paramothayan NS, Lasserson TJ, Jones PW. Corticosteroids for pulmonary sarcoidosis. Cochrane Database Syst Rev 2005: p. CD001114.
74 Sollberger M, et al. Successful treatment of steroid-refractory neurosarcoidosis with infliximab. J Neurol 2004;251:760–1.
75 Yee AM, Pochapin MB. Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-alpha therapy. Ann Intern Med 2001;135:27–31.
76 Baughman RP, Lower EE. Infliximab for refractory sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2001;18:70–4.

77 Baughman RP, et al. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. Chest 2005;128: 1062–47.
78 Utz JP, et al. Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. Chest 2003;124:177–85.
79 Khanna D, Liebling MR, Louie JS. Etanercept ameliorates sarcoidosis arthritis and skin disease. J Rheumatol 2003;30:1864–7.
80 Kolopp-Sarda MN, et al. Discriminative immunophenotype of bronchoalveolar lavage CD4 lymphocytes in sarcoidosis. Lab Invest 2000;80:1065–9.
81 Spagnolo P, et al. C-C Chemokine Receptor 5 Gene Variants in Relation to Lung Disease in Sarcoidosis. Am J Respir Crit Care Med 2005:172:721–8.
82 Agostini C, et al. Role for CXCR6 and its Ligand CXCL16 in the Pathogenesis of T-cell Alveolitis in Sarcoidosis. Am J Respir Crit Care Med 2005.
83 Valentonyte R, et al. Sarcoidosis is associated with a truncating splice site mutation in BTNL2. Nat Genet 2005;37:357–64.
84 Rybicki BA, et al. The BTNL2 Gene and Sarcoidosis Susceptibility in African Americans and Whites. Am J Hum Genet 2005;77:491–9.
85 Rutherford RM, et al. Functional genomics and prognosis in sarcoidosis – the critical role of antigen presentation. Sarcoidosis Vasc Diffuse Lung Dis 2004;21:10–8.
86 Bihl MP, et al. Progressive pulmonary sarcoidosis – a fibroproliferative process potentially triggered by EGR-1 and IL-6. Sarc Vasc Lung Dis 2005: p. In press.
87 Chang B, et al. Depression in sarcoidosis. Am J Respir Crit Care Med 2001;163:329–34.
88 Yeager H, et al. Pulmonary and psychosocial findings at enrollment in the ACCESS study. Sarcoidosis Vasc Diffuse Lung Dis 2005;22:147–53.
89 Brutsche M. MEDICA-Seminar-Beitrag: Lebensqualität und medizinische Betreuung bei Sarkoidose – die Meinung der Betroffenen. Sarkoidose Nachrichten und Berichte, 2002.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

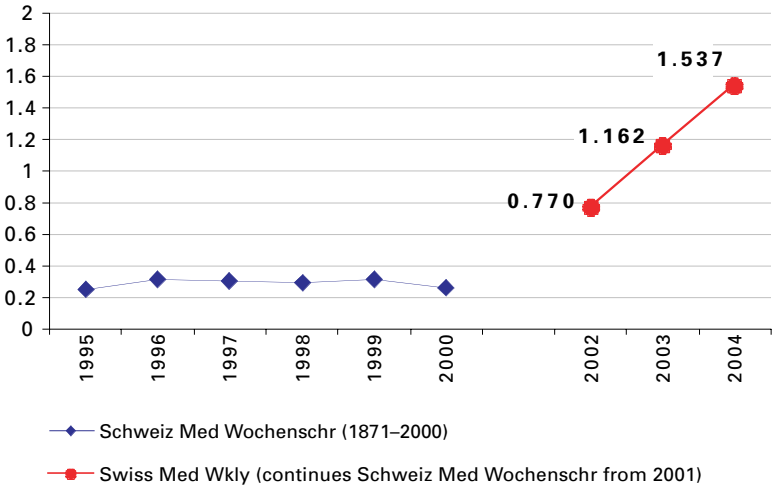
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch