

OPTIMIZING TREATMENT
AND OUTCOMES FOR
PATIENTS WITH
SARCOIDOSIS



Vivienne Kahlmann

Optimizing Treatment and Outcomes for Patients with Sarcoidosis

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Optimaliseren van behandeling
en uitkomsten voor patiënten met sarcoïdose

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Optimizing treatment and outcomes for patients with sarcoidosis

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Promotor:	Prof.dr. M.S. Wijsenbeek-Lourens
Copromotor	Dr. C.C. Moor
Beoordelingscommissie:	Prof.dr. M. Drent Prof.dr. F. Bonella Dr. P.L.A. van Daele

Table of Contents

PART I INTRODUCTION		
Chapter 1	General introduction	11
Chapter 2	Comprehensive Care for Patients with Sarcoidosis <i>J Clin Med. 2020 Feb; 9(2): 390.</i>	23
PART II IMPROVING PHARMACOLOGICAL TREATMENT FOR PATIENTS WITH SARCOIDOSIS		
Chapter 3	Comparison of the treatment guidelines for sarcoidosis: common sense in the search of evidence <i>Eur Respir J. 2022 Feb 10;59(2):2103114.</i>	49
Chapter 4	Patient-reported side effects of prednisone and methotrexate in a real-world sarcoidosis population <i>Chron Respir Dis. 2021 Jan-Dec;18:14799731211031935.</i>	61
Chapter 5	COVID-19 infection in patients with sarcoidosis: susceptibility and clinical outcomes <i>Curr Opin Pulm Med. 2021 Sep 1;27(5):463-471.</i>	73
Chapter 6	Design of a randomized controlled trial to evaluate effectiveness of methotrexate versus prednisone as first-line treatment for pulmonary sarcoidosis: the PREDMETH study <i>BMC Pulm Med. 2020 Oct 19;20(1):271.</i>	97
Chapter 7	First-Line Treatment of Pulmonary Sarcoidosis with prednisone or methotrexate <i>New England Journal of Medicine. 2025 Jul 17;393(3):231-242.</i>	117
PART III IMPROVING QUALITY OF LIFE FOR PATIENTS WITH SARCOIDOSIS		
Chapter 8	Non-Organ-Specific Manifestation of Sarcoidosis <i>Sarcoidosis (ERS Monograph). 2022; pp. 206–222.</i>	171
Chapter 9	Managing fatigue in patients with interstitial lung disease <i>Chest 2020 May 7;158(5):2026–2033.</i>	201

Chapter 10	Online mindfulness-based cognitive therapy for fatigue in patients with sarcoidosis (TIRED): a randomized controlled trial <i>Lancet Respiratory Medicine 2023 Mar;11(3):265-272.</i>	221
Chapter 11	Sarcoidosis and fatigue: there is a useful cognitive treatment? - Authors' reply <i>Lancet Respiratory Medicine 2023 Jul;11(7):e67.</i>	251
Chapter 12	Innovating care for people with sarcoidosis using a machine learning-driven approach <i>Respir. Res. 2025: Jun 19;26(1):218.</i>	255

PART IV | DISCUSSION

Chapter 13	General discussion	275
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PART V | APPENDICES

Summary	306
Samenvatting	312
PhD portfolio	320
List of publications	326
About the author	330
Dankwoord	332

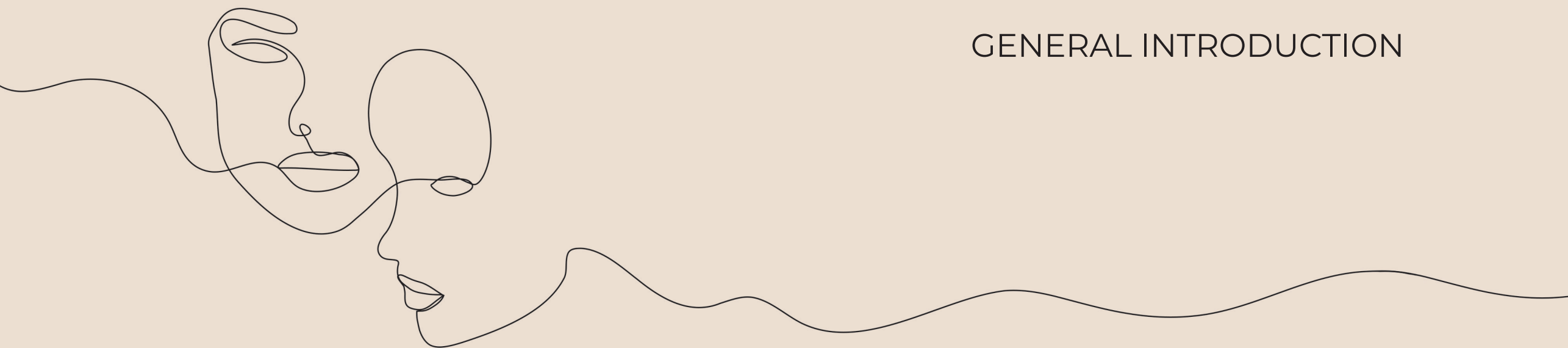
The background is an abstract composition of layered, textured paper. A large, light beige piece of paper is at the top, with a smaller, darker beige piece layered underneath it on the right. In the lower-left, there's a large, vibrant pinkish-red watercolor wash. To its left, a smaller, muted purple-grey wash is visible. In the bottom-right corner, there's another wash of deep red. Scattered across the entire composition are numerous small, circular watercolor splatters in various shades of pink, red, and beige, creating a sense of movement and artistic spontaneity.

Part I

INTRODUCTION

Chapter 1

GENERAL INTRODUCTION



General introduction

Sarcoidosis

Sarcoidosis is a complex multisystem inflammatory disease, characterized by granuloma formation that can affect almost any organ (1). Sarcoidosis can present with a wide range of symptoms depending on the organ involved, with patterns of involvement differing by race.

The lungs and lymphatic system are most commonly involved, affecting up to 95% of patients (2). Patients with pulmonary sarcoidosis may experience symptoms, such as cough, dyspnea or chest pain. Cutaneous sarcoidosis is also relatively common, reported in up to 16% of patients, and may manifest with a wide range of skin lesions, from small papules to broader plaques (3). Although less common, cardiac and neurosarcoidosis are important because of the risk of more severe and potentially life-threatening complications. Clinically manifest cardiac sarcoidosis is reported in approximately 5%, however imaging and autopsy studies suggest that cardiac involvement may be present in 25% of patients. Patients may present with symptoms such as dyspnea, palpitations, syncope, rhythm abnormalities (4). Neurosarcoidosis, occurring in up to 9% of patients, can present with a variety of neurological symptoms including cranial neuropathy, meningitis and encephalopathy (5). In addition to organ-specific symptoms, patients often experience non-organ-specific symptoms, such as fatigue, cognitive decline and anxiety. Notably, these symptoms may also be present if there are no signs of disease activity. The heterogeneity of the disease requires a comprehensive and multidisciplinary approach to care (6).

Etiology of sarcoidosis

Although the cause of sarcoidosis remains unknown, progress has been made in understanding its underlying disease mechanisms. Both genetic susceptibility and environmental factors seem to play a key role in the pathogenesis of sarcoidosis (1). It is hypothesized that an unknown antigen triggers an inflammatory response in genetically predisposed individuals, leading to activation of both the innate and the adaptive immune system, resulting in cytokine release and finally granuloma formation (**Figure 1**). After sarcoidosis develops, the clinical course and prognosis are highly variable. It is estimated that, around 70% of patients will experience remission, with or without treatment, whereas 30% develop chronic sarcoidosis, which in some patients will result in fibrotic sarcoidosis. Currently, predictive models to identify individual patients at risk of a more progressive course at baseline are lacking, although certain factors have been associated with

prognosis (6). Löfgren's syndrome, a form of sarcoidosis characterized by acute onset of bilateral hilar lymphadenopathy, erythema nodosum, and arthritis, is associated with a favorable prognosis, particularly in patients carrying the human leucocyte antigen (HLA) DRB1*03 (7). In contrast, other HLA variants are linked to less favorable outcomes (6). In addition to genetic factors, certain demographic characteristics are associated with prognosis. Early onset of the disease, before the age of 40 years, is generally linked to a more favorable outcome. In contrast, older age and Black patients, especially females, have been associated with a higher risk of chronic or severe disease (8). Unsurprisingly, patients with more severe pulmonary involvement, signs of fibrosis or pulmonary hypertension tend to have a less favorable prognosis (9). Furthermore, certain extra-pulmonary manifestations, such as lupus pernio (blue-purple colored skin lesions affecting the nose), cardiac involvement, and hypercalcemia are associated with more severe disease (10).

Epidemiology

Sarcoidosis can occur in any individual at any age. The incidence and prevalence vary around the world, largely due to variations in ethnicity and age distribution across populations. Sarcoidosis is more common in women than in men. The peak incidence occurs between the ages of 40 and 59 years in men, and between 50 and 69 years for women (12-14). Black individuals are approximately twice as likely to develop sarcoidosis compared to white individuals (15). In addition to demographic variation, several risk factors are associated with developing sarcoidosis, including genetic, environmental, occupational, and lifestyle factors. Although sarcoidosis is not considered a heritable disease, first-degree family members of affected individuals have an increased risk of developing sarcoidosis (16, 17). A large case-control study identified multiple factors associated with a higher risk of sarcoidosis, including exposure to insecticides, inorganic or organic material (e.g. in agricultural employment), and working in moldy and dusty environments (18). Obesity, which contributes to a pro-inflammatory state, is associated with an increased risk of developing sarcoidosis (14, 19).

Diagnostic approach

Diagnosing sarcoidosis can be challenging, as patients can present with a wide range of different symptoms. There is no gold standard test to fully secure the diagnosis, as sarcoidosis is a diagnosis of exclusion. The diagnosis is based on three major criteria: compatible clinical and radiological features, histological evidence of granulomatous inflammation, and exclusion of other conditions (e.g. tuberculosis, lymphoma, common variable immune deficiency) (20). In

the majority of patients, a biopsy is needed to support the diagnosis. Typical histological findings are non-necrotizing granulomas, however occasionally (<15%) necrotizing granulomas are observed. In some patients with a high suspicion of sarcoidosis, based on typical clinical and radiological features, a biopsy is not required. This concerns patients with Löfgren's syndrome, lupus pernio, and Heerfordt's syndrome (a rare manifestation of sarcoidosis, characterized by anterior uveitis, enlargement of parotid or salivary glands and cranial nerve palsy).

For pulmonary sarcoidosis, the Scadding radiographic staging system, first introduced in 1961, is the most commonly used classification (21). It categorizes chest radiographs into the following different stages:

- Stage 0: No abnormalities
- Stage 1: Bilateral hilar lymphadenopathy without parenchymal involvement
- Stage 2: Bilateral hilar lymphadenopathy with parenchymal abnormalities
- Stage 3: Parenchymal abnormalities without bilateral hilar lymphadenopathy
- Stage 4: Pulmonary fibrosis, with or without lymphadenopathy

Although this staging system is widely used, it has several limitations. These include large interobserver variability, underestimation of the presence of parenchymal abnormalities compared to chest CT, poor correlation with pulmonary function tests, and poor correlation with prognosis, particularly for stage II and III (22-25). Due to these limitations, a chest CT scan is generally conducted in all patients with sarcoidosis to provide a more accurate assessment of pulmonary involvement (26).

Pharmacological treatment

Around half of the patients with pulmonary sarcoidosis do not require treatment since spontaneous remission can occur, especially in patients with limited symptoms and absence of significant pulmonary function impairment. The decision whether to start treatment or not can be challenging. There are no exact threshold values for pulmonary function tests indicating the need to start treatment. In general, treatment is indicated in patients with pulmonary involvement at risk of mortality or permanent disability, or severe symptoms (27). Hence, as no one-size-fits-all approach exists, the decision to initiate treatment requires a shared decision-making process between physicians and patients, carefully weighing the benefits of immunosuppressive treatment against possible side effects.

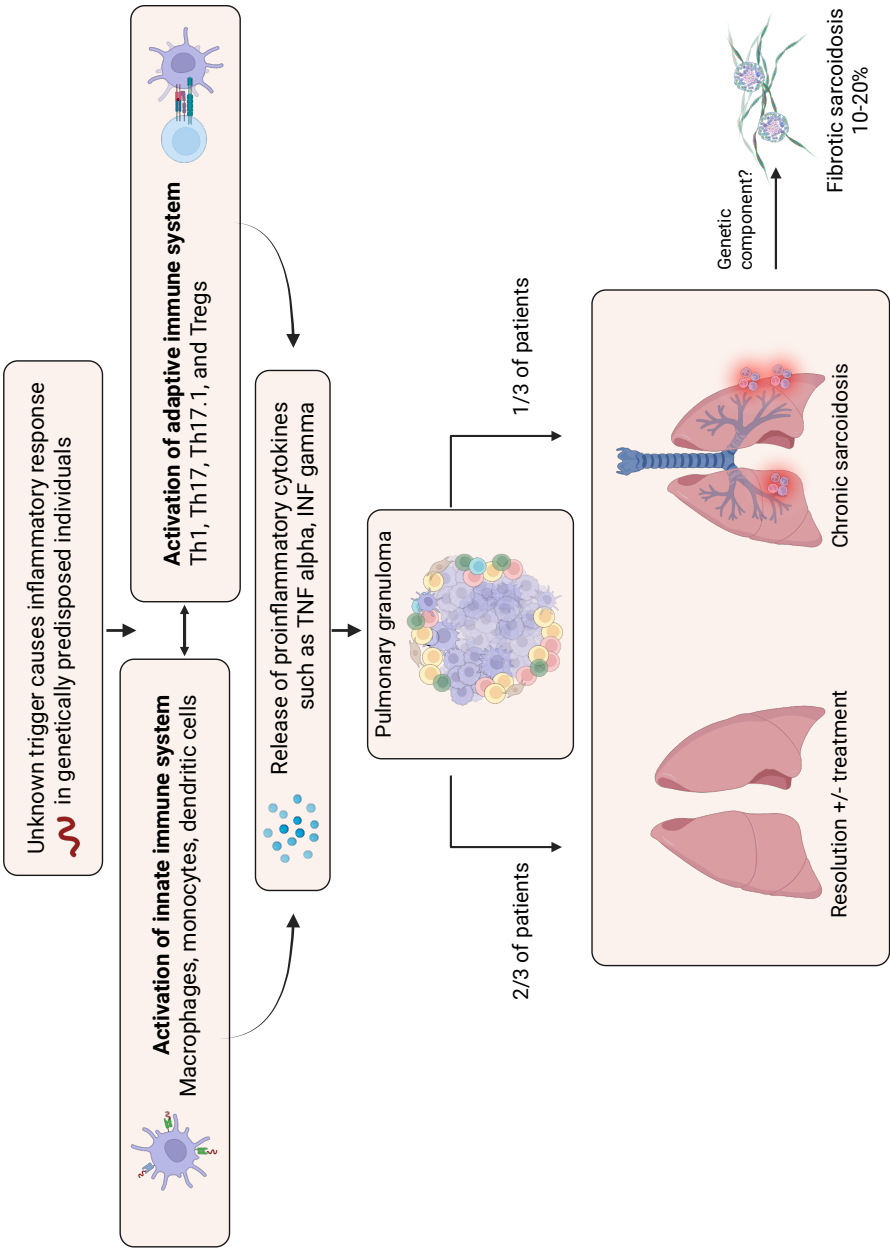


Figure 1. Simplified overview of the pathogenesis and prognosis of sarcoidosis: from immune activation to clinical outcomes

Current treatment strategies for pulmonary sarcoidosis are based on a step-up approach (2, 27). The mainstay pharmacological treatment for pulmonary sarcoidosis is prednisone. Although prednisone has been the first choice for treatment for many years, high-quality evidence to support this recommendation is lacking. Prednisone improves symptoms, radiology, and pulmonary function tests in the short term, however, it is still debated if prednisone alters the natural disease trajectory in the long term (e.g. slowing down disease progression and prevention of fibrosis) (28). Prednisone use is often accompanied by burdensome side effects, such as weight gain, osteoporosis, and psychological symptoms, especially in case of long-term use (29-31). The first aim of this thesis was to optimize immunosuppressive treatment for patients with sarcoidosis.

Quality of life

Another major clinical challenge in daily practice is the management of non-organ-specific manifestations of sarcoidosis, which can significantly impact the daily lives of patients and partners (32-34). Especially fatigue is highly prevalent and strongly related to quality of life (QoL) in patients with sarcoidosis. The etiology of fatigue is complex, involving multiple contributing factors, such as physical, psychological and behavioural factors (35). Fatigue does not correlate well with clinical parameters and often persists in patients without signs of active inflammatory disease (36, 37). Several studies have shown that pulmonary rehabilitation and physical training programs improve fatigue and quality of life (38-41). Although a high correlation has been found between fatigue and psychological symptoms, studies investigating the effect of psychological interventions in patients with sarcoidosis were lacking until now. The second aim of this thesis was to look for strategies to improve quality of life.

General outline and aims of this thesis

The thesis focuses on optimizing treatment and outcomes for patients with sarcoidosis.

Part I: Introduction

Part I contains a general introduction to sarcoidosis (**Chapter 1**). In **Chapter 2**, we summarized current literature and proposed a structured approach to improve comprehensive sarcoidosis management.

Part II: Improving pharmacological treatment for patients with sarcoidosis

In 2021, the European Respiratory Society (ERS) guideline on the treatment of sarcoidosis was published. Unfortunately, all recommendations were based on very low to low quality of evidence, highlighting the need for more high-quality research. In **Chapter 3**, we described our perspectives on future study designs, emphasizing the need for other first-line treatment options, as prednisone is often accompanied by burdensome side effects. Based on physician experience in clinical practice, methotrexate, commonly used as a second-line treatment, seemed to have fewer side effects than prednisone. To explore whether methotrexate is better tolerated, we assessed patient experiences with medication use by comparing the side effect profiles of prednisone and methotrexate in a real-world sarcoidosis population (**Chapter 4**). During the conduct of the studies in this thesis, the coronavirus disease 2019 (COVID-19) pandemic emerged with major implications for healthcare in general, particularly for patients with chronic diseases using immunosuppressive treatment. As there was much uncertainty about the impact of COVID-19 infections in patients with sarcoidosis, we reviewed the current knowledge about susceptibility and clinical outcomes. These findings are described in **Chapter 5**. In **Chapter 6**, we described the study protocol of the PREDMETH trial, a non-inferiority randomized controlled trial in 17 centers in the Netherlands, investigating the effectiveness and tolerability of prednisone compared with methotrexate. In **Chapter 7**, we present the results of the PREDMETH trial.

Part III: Improving quality of life for patients with sarcoidosis

Patients with sarcoidosis often face significant challenges, including underrecognized non-organ-specific manifestations, which can greatly impact their daily lives. In **Chapter 8**, we describe the impact of non-organ-specific manifestations and advocate for a comprehensive, multidisciplinary approach to treatment. In **Chapter 9**, we focus on the management of fatigue in patients

with sarcoidosis and other interstitial lung diseases. Together with the Dutch sarcoidosis patient organization, the idea for the TIRED trial was conceived. In the TIRED trial we investigated the effectiveness of online mindfulness-based cognitive therapy for fatigue in patients with sarcoidosis (**Chapter 10**). In **Chapter 11**, we provided an algorithm for the assessment and management of fatigue in patients with sarcoidosis. In the last chapter, we explore a novel machine learning methodology, called patient journey mapping, to better understand patient experiences (**Chapter 12**).

Part IV: General discussion

Part IV contains the general discussion (**Chapter 13**), in which the main findings of this thesis are discussed in the context of existing literature. Furthermore, future directions for research are discussed.

Together, the chapters of this thesis aim to optimize treatment and outcomes for patients with sarcoidosis by contributing to more evidence-based, personalized, comprehensive and patient-centered care.

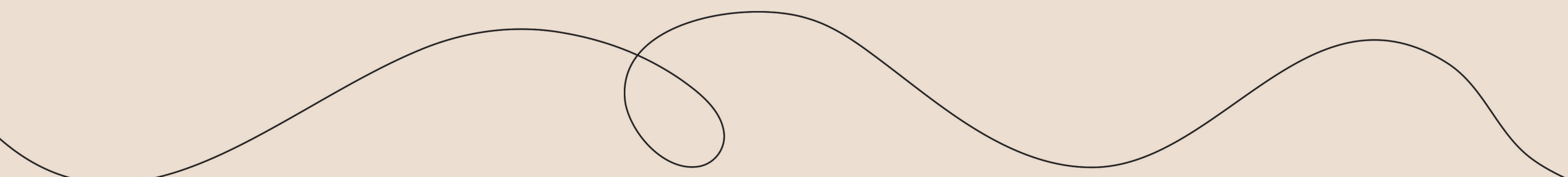
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Chapter 2

Comprehensive Care for Patients with Sarcoidosis



J Clin Med. 2020 Feb; 9(2): 390.

Catharina C. Moor, Vivienne Kahlmann, Daniel A. Culver, Marlies S. Wijsenbeek

1. Department of Respiratory Medicine, Erasmus Medical Center Rotterdam, 3015 GD Rotterdam, The Netherlands
2. Department of Pulmonary Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, OH 44195, USA

Abstract

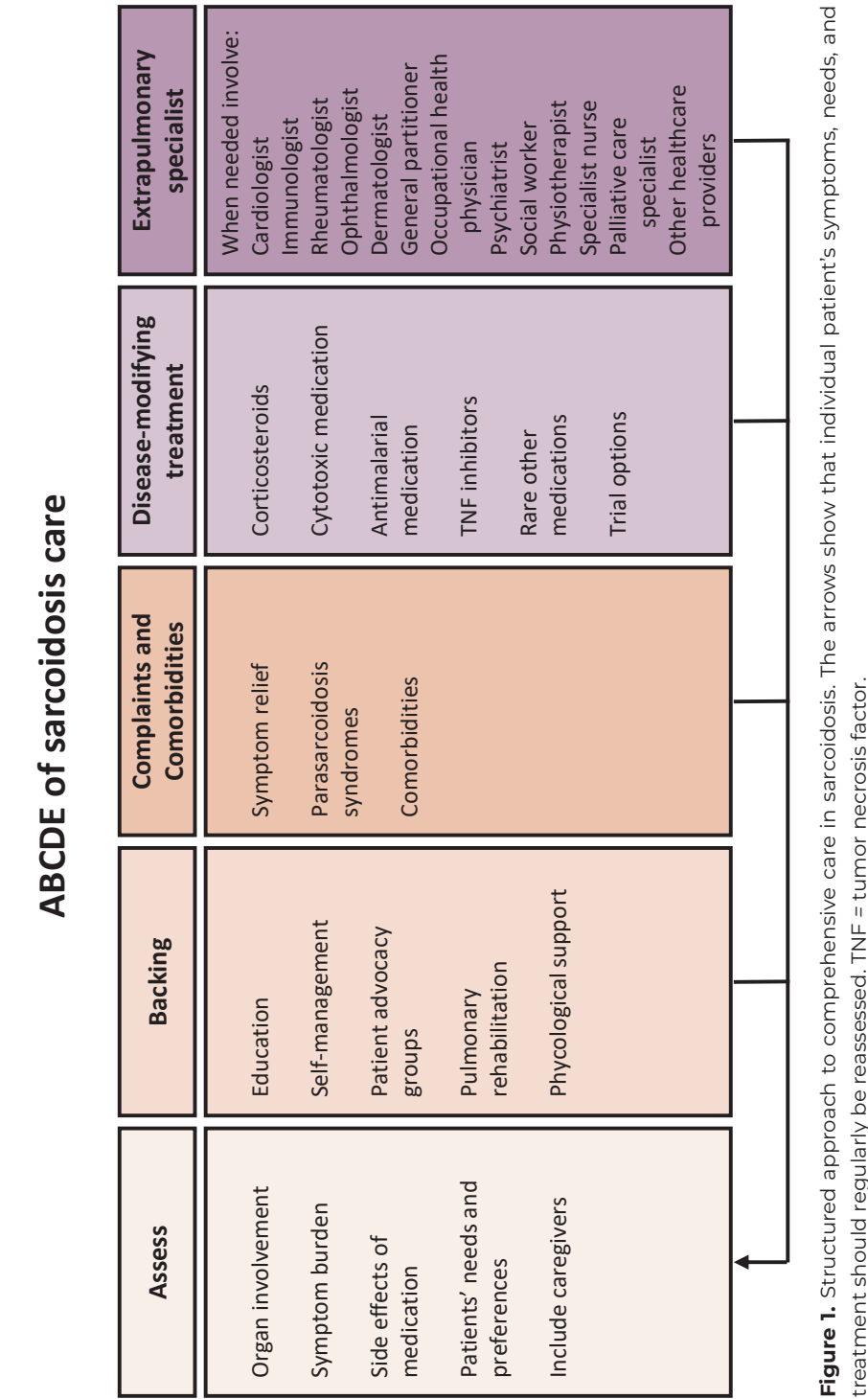
Sarcoidosis is a multisystem granulomatous disease, associated with significant morbidity and impaired quality of life. Treatment is aimed at recovering organ function, reducing symptom burden and improving quality of life. Because of the heterogeneity and variable disease course, a comprehensive, multidisciplinary approach to care is needed. Comprehensive care includes not only pharmacological interventions, but also supportive measures aimed at relieving symptoms and improving quality of life. The purpose of this review is to summarize the most recent knowledge regarding different aspects of care and propose a structured approach to sarcoidosis management.

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown cause, that can affect almost any organ. The past decade we have gained more insights in the dysregulation of the immune system, which is thought to play an important role in the etiology of sarcoidosis (1). Patients may present with a wide range of organ-specific symptoms, such as cough and dyspnea, or non-organ manifestations including fatigue, depression, and reduced exercise tolerance (1). In about 60 percent of patients, remission occurs spontaneously or after treatment within 10 years after diagnosis (2). In approximately 10–40% of patients, sarcoidosis becomes chronic and progressive. Mortality is around 1–5%, and is higher in African-American patients and elderly patients (3). In general, sarcoidosis leads to a substantial economic burden and societal impact, mainly because of hospitalizations, medication costs and the inability to work (3,4). For individual patients, high symptom burden often leads to psychological problems and an impaired quality of life (QoL) (5).

Current pharmacological treatment of sarcoidosis is usually immunosuppressive and directed at decreasing granulomatous inflammation (2). Overall, treatment is aimed at recovering organ function, reducing symptom burden and improving quality of life (6). Pharmacological interventions are not curative and—in a subgroup of patients—symptoms or disease progression may persist (2). A comprehensive approach to care is needed for patients with sarcoidosis, especially because of the heterogeneity in symptoms and organ involvement and variable disease course (7). This review is written from a pulmonologist's perspective, as in many hospitals the pulmonologist is the central care coordinator. However, we would like to stress the importance of multidisciplinary care as extrapulmonary disease is present in the majority of patients.

The aim of this review is to summarize the most recent knowledge regarding different aspects of care in sarcoidosis and propose the “ABCDE model for sarcoidosis”, which is an adaptation of the version in interstitial lung diseases (ILD) (10,11).



ABCDE Model

The importance of comprehensive care in sarcoidosis is generally acknowledged (12,13). Here, we describe the ABCDE model, that can be used to structure comprehensive sarcoidosis management in order to improve QoL and outcomes for patients (**Figure 1**). This model includes the following components: the **A**ssessment of symptoms and patient's needs, **B**acking patients by providing support and education, treatment of **C**omplaints and **C**omorbidities, **D**isease-modifying treatment, and the involvement of **E**xtrapulmonary specialists. As disease activity, organ involvement, and patients' preferences may vary during the disease course, regular reassessment is essential. The ABCDE model can provide guidance to clinicians during the first work-up and follow-up of patients with sarcoidosis. Different components of the model are discussed in more detail in the following paragraphs.

Assess

In all patients with sarcoidosis, organ involvement should be carefully assessed in the diagnostic process and during follow-up. The degree of organ damage and disease activity is often difficult to quantify, as no gold standards exist and symptoms are often non-specific (3,14,15). Reported percentages of organ involvement are wide ranging, depending on whether only clinically overt organ involvement or also asymptomatic organ involvement is taken into account. For example, 2%–5% of patients have symptomatic cardiac involvement, but the frequency of clinically inapparent involvement is much higher (probably up to 25%) (9).

Furthermore, organ involvement significantly varies for different ethnic groups. In individual patients, the number of involved organs may change over time and therefore diagnostic assessments have to be performed regularly, particularly if patients express new symptoms (1,16). The frequency in which different organ systems are affected in sarcoidosis is summarized in **Figure 2** (1,9). Consequently, patients without apparent organ involvement could still have a high symptom burden (13). Hence, Drent et al. proposed four different domains that should be evaluated in the complete work-up of a patient; not only the severity, extent and activity of the disease, but also the impact of disease (13). In a recent survey with over 1000 respondents, 95% of patients reported sarcoidosis-related symptoms, and self-reported symptom burden of sarcoidosis was high (17). Due to this high symptom burden, uncertain prospects, and sometimes social isolation and inability to work, sarcoidosis has a huge impact on lives of patients (3,13,18). In a Dutch government survey, more than 60% of sarcoidosis patients

(n= 150) considered their general health moderately to severely impaired. Only 7% answered that their health problems had no influence on their social life (19). Furthermore, almost 50% of patients in a recent study (n = 755) were partially or totally unable to work due to their sarcoidosis, highlighting the considerable impact of sarcoidosis on daily life (18). A Swedish national registry evaluation of 3347 sarcoidosis patients aged 25–59 years, suggested 8% lower income and 26 lost workdays in the year of diagnosis compared with age matched controls (20). In a US registry (n = 2318), 44% of respondents reported a large effect on household finances, and 31% had to quit their job after the diagnosis of sarcoidosis (4).

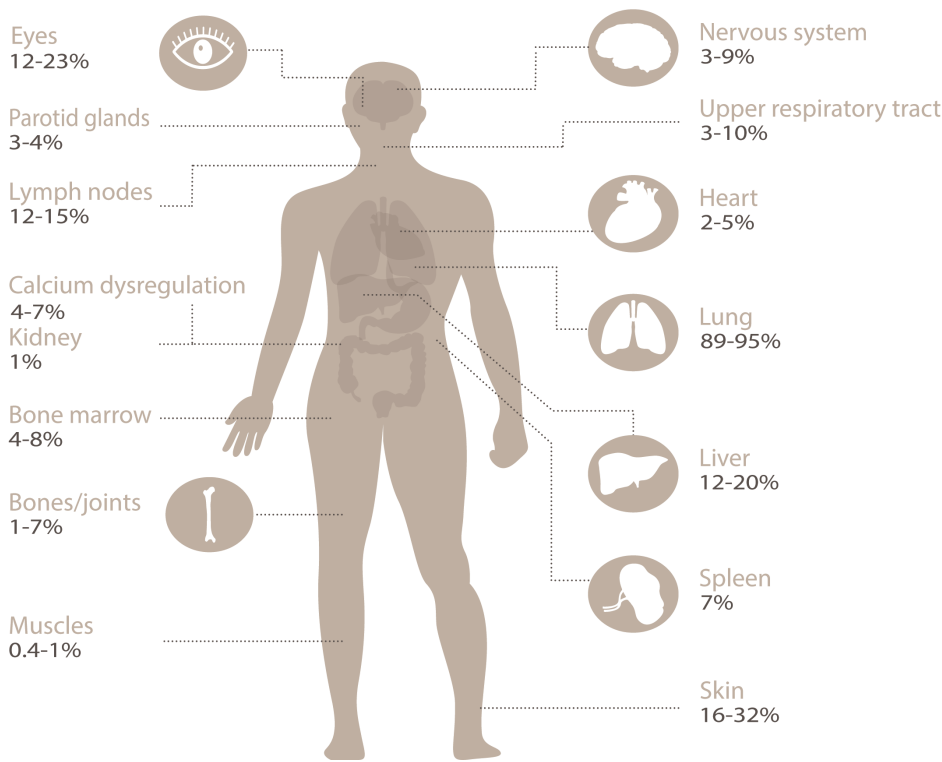


Figure 2. Organ involvement in sarcoidosis. Organ involvement is classified according to the ACCESS organ assessment instrument (8). Prevalence data are used from references (1,9).

Overall, sarcoidosis patients have an impaired QoL compared with the healthy population (5). Several studies analyzed the relation between symptoms and QoL in sarcoidosis. Symptoms predictive for QoL are depression, anxiety, fatigue, reduced exercise capacity, small fiber neuropathy (SFN)-related symptoms,

dyspnea, pain, and arthralgia (15,21–26). Interestingly, partners of sarcoidosis patients also experience a reduced QoL compared with healthy controls (21). Moreover, partners tend to have increased anxiety levels and psychological distress (27). Both patients as well as their partners reported that there should be more support for partners of sarcoidosis patients (27).

QoL can be defined as “an individual’s perception of their position in life” and is influenced by a person’s values, beliefs, culture, physical health, social and psychological state (28). QoL can be measured with patient-reported outcome measures (PROMs). PROMs are instruments that “collect self-reported information about a patients’ health condition, without any intervention from a healthcare provider” (29). PROMs can be either generic (applicable to the whole population), disease-specific (developed or validated in a specific disease) or domain-specific (assessing severity or burden of a specific symptom or organ). A wide range of PROMs are currently being used for sarcoidosis (30,31). A number of these instruments, such as the King’s Sarcoidosis Questionnaire (KSQ), Sarcoidosis Health Questionnaire (SHQ), Sarcoidosis Assessment Tool (SAT), and Fatigue Assessment Scale (FAS) have been specifically developed to measure QoL and symptom burden in sarcoidosis (31–34). Although PROMs are mainly used in clinical trials, well-validated PROMs could also be used in clinical practice to evaluate treatment effect and longitudinal changes in symptoms and QoL (31,35). In other chronic diseases, the use of PROMs in regular care is associated with enhanced communication and shared-decision making, detection of unrecognized problems, higher patient satisfaction and improved QoL (36,37). Future research could affirm whether this is also the case in sarcoidosis.

Other factors with a potential negative impact on QoL should not be forgotten in the assessment of patients with sarcoidosis. For example, medication for sarcoidosis may lead to debilitating side effects, such as weight gain, diabetes, osteoporosis and psychological problems (38–40). According to one study, patients with higher cumulative doses of prednisolone had a significantly lower QoL when adjusted for disease severity (4,39). Moreover, medication-related events lead to a substantial number of hospitalizations in patients with sarcoidosis (41). Consequently, (dis)advantages of starting and continuing therapy should be weighted by the healthcare provider and patient during every clinic visit.

Although it is increasingly acknowledged that patient perspectives are important for optimizing individually-tailored treatments (17,27,42), literature concerning (unmet) needs and preferences of patients with sarcoidosis is scarce. Recently,

an international survey revealed that sarcoidosis patients considered QoL and functionality as the most important treatment outcomes (7). Blood tests and pulmonary function tests were considered the least important outcomes (7). These results are in contrast to the current focus of most clinicians on physiological outcome measures (5,15,17,30). In a number of studies, patients reported the need for better information about sarcoidosis and shared decision making (19,27). As treatment goals can obviously differ between patients, the first step in shared-decision making is identifying patients' needs and preferences. During the disease course, patients should be involved in their treatment plan and in the regular evaluation of benefits versus risks of (pharmacological) treatment (12,16,19). Including patients as a partner in care could lead to better QoL and adherence to treatment (43,44). Multidisciplinary management and improved access to sarcoidosis specialists and expert centers for sarcoidosis are other important needs for patients, although it must be acknowledged that not all sarcoidosis patients require tertiary care (7,27).

Backing

Several support measures to improve QoL for sarcoidosis patients have been suggested in the past years. Better information and education are vital to optimize care for sarcoidosis (13,18,27,45,46). Even in the current internet era, patients state that they cannot find enough reliable information about their disease online (19,27). Moreover, the complexity and heterogeneity of sarcoidosis may complicate communication and knowledge transfer between healthcare providers and patients (13). Currently, patients and their partners often feel misunderstood because of a lack of knowledge among healthcare providers and the general public (13,27). Hence, awareness should be raised in society and among relevant healthcare providers. Patient advocacy groups could play an important role in providing understandable information and education, by organizing information meetings and awareness campaigns (47). Although support groups can have obvious benefits, effects on QoL have never been studied in sarcoidosis.

Self-management support is one of the main pillars of the chronic care model, developed to improve care for patients with chronic conditions (48). Many aspects of chronic disease care can only be managed by patients themselves. Self-management strategies cover all disease domains, and include for example behavioural changes, medication use, exercise, dietary strategies and home monitoring of disease (49,50). To achieve skills for self-management, patients and families need to be adequately trained and supported by their healthcare providers (1). Use of novel eHealth solutions to enhance self-management has recently gained interest in sarcoidosis (45,51). Self-monitoring of symptoms, side

effects, QoL, activity and pulmonary function at home has shown to be feasible and highly appreciated by patients with sarcoidosis (51,52). A comprehensive home monitoring program may provide patients with more insights in their disease course, and thereby empower patients and enhance communication with healthcare providers. In a recent study, home monitoring of pulmonary function allowed for earlier detection of steroid treatment effects, suggesting that patient-managed steroid dosing regimens may be feasible (52).

While activity tracking at home could possibly help to stimulate exercise (51,53–55), supervised training programs or multidisciplinary pulmonary rehabilitation might have more beneficial effects (13). Current evidence indicates that a structured, supervised exercise program can improve symptoms, QoL, exercise capacity, and muscle strength in patients with different stages of sarcoidosis (56–61). Although these studies showed promising results, no evidence-based guidelines exist to date. In a survey of international sarcoidosis experts, the vast majority of respondents considered physical training in sarcoidosis valuable and would recommend it as standard of care (56). Pulmonary involvement, fatigue, and reduced exercise tolerance are the main indications for physical therapy in sarcoidosis (56). The long-term effects of physical therapy, optimal duration and content of exercise programs in sarcoidosis have never been investigated and need further study. Furthermore, reimbursement and distance to appropriate exercise programs vary between regions and countries and may limit access to physical therapy for sarcoidosis patients (56). Telerehabilitation could potentially be a solution for patients living in rural areas because distances are bridged online. A study evaluating the feasibility and effect of a telerehabilitation program in sarcoidosis is ongoing (NCT03914027).

The majority of patients would like to have better access to psychological support (7,27). In clinical practice, patients are referred to a psychologist or psychiatrist for further counseling and treatment on indication, though some people advocate for standard psychological assessment (62). Cognitive behavioural therapy has been proposed as a promising method to offer psychological support; this therapy could potentially improve patients' coping strategies and thereby reduce stress, anxiety and depression (13,23). To date, one study analyzed the impact of mindfulness-based exercise therapy on physical and psychological symptoms in sarcoidosis. Even though this was a modified training consisting of only one 45-minute workshop, symptoms significantly decreased after the session (63). A randomized controlled trial to assess the impact of an online mindfulness-based cognitive behavioural therapy on QoL, fatigue, stress, and anxiety is currently ongoing (64).

Complaints and Comorbidities

Symptom relief is a major aspect of sarcoidosis management. Dyspnea is among the most common symptoms in sarcoidosis and is an important indication for treatment (12). Dyspnea is often multifactorial and can be caused by pulmonary, musculoskeletal or cardiac involvement of sarcoidosis, or deconditioning. Other causes for dyspnea such as infection or pulmonary hypertension should also be evaluated (12). Non-pharmacological treatment options include physical training, multidisciplinary pulmonary rehabilitation and potentially cognitive behavioural therapy (58–60,63) (**Table 1**). Cough is present in up to 53% of sarcoidosis patients (65). Patients with sarcoidosis have a significantly higher cough frequency compared with the normal population (66). Even though cough is often part of the disease, other causes such as reflux or post-nasal drip should always be excluded. One study showed that inhaled corticosteroids may be effective in reducing cough in sarcoidosis, but two other small studies showed no effects of inhaled corticosteroids on cough in sarcoidosis (67–69). Consequently, inhaled corticosteroids should not be routinely administered unless a trial demonstrates efficacy (70). In the recent CHEST guideline, speech therapy is recommended for patients with ILD and refractory cough, however, this therapy has not been specifically evaluated in sarcoidosis (70). Vasoactive intestinal peptide (VIP) inhalation seemed to reduce cough in sarcoidosis in one small open clinical phase II study, but has never been investigated in a randomized setting (71). Further studies regarding antitussive therapy in sarcoidosis are highly needed.

Non-organ manifestations or parasarcoidosis syndromes include symptoms as fatigue, depression, anxiety, pain, SFN, and cognitive impairment (46). As most of these symptoms are related to each other, it can be challenging to avoid a vicious circle. Fatigue is one of the most prevalent (up to 90% of patients) and burdensome symptoms for patients with sarcoidosis (17,27). Fatigue is a complex, multifactorial problem (13). Symptoms as sleep disturbance, psychological problems, cognitive impairment, reduced exercise capacity, and muscle strength are all linked to fatigue (77–81). Moreover, comorbidities and medication use may also contribute to fatigue. Previously, it has been shown that patients with multi-organ involvement and a higher number of comorbidities have increased fatigue levels (78). Comorbidities associated with fatigue are sleep apnea, pulmonary hypertension, diabetes mellitus, thyroid disorders, and obesity (78). Fatigue is often a chronic problem, which persists or worsens despite sarcoidosis treatment. Research into better pharmacological and non-pharmacological treatment options for sarcoidosis-associated fatigue is scarce. Two small randomized trials demonstrated that neurostimulants (armodafinil and methylphenidate) have

the potential to reduce sarcoidosis-associated fatigue (72,73). A number of other relatively small or retrospective studies showed the benefits of physical training and cognitive behavioural therapy on fatigue in sarcoidosis (57–60,63). Larger studies investigating the etiology and better treatment options for sarcoidosis-associated fatigue are essential to improve symptom burden and QoL for patients.

Table 1. Overview of pharmacological and non-pharmacological treatment options for common sarcoidosis symptoms. Many of these recommendations are expert opinion or based on small studies.

Symptom	Pharmacological Treatment	Non-Pharmacological Treatment
Dyspnea	Regular disease-modifying treatment Treat other causes Supplemental oxygen (in case of hypoxemia)	Physical training, pulmonary rehabilitation (58,59,60) Cognitive behavioral therapy (63)
Cough	Regular disease-modifying treatment Treat other causes Inhaled corticosteroids *	Multimodality speech pathology therapy (70)
Fatigue	Treat other causes and comorbidities Neurostimulants: armodafinil, (dex)methylphenidate (72,73) TNF inhibitor treatment (74)	Treat reversible causes i.e., obstructive sleep apnea, obesity, depression Physical training or pulmonary rehabilitation (57,58,59,60) Psychosocial counselling (13) Cognitive behavioral therapy (63)
Depression and Anxiety	Antidepressants (13) ** Anxiolytics **	Cognitive behavioral therapy (63) Pulmonary rehabilitation (58) Psychological counselling (46)
Small-Fiber Neuropathy	Antidepressants Anticonvulsants Topical anesthetics Opioids (46) Intravenous immunoglobulin (75,76) TNF inhibitor treatment (76)	Mindfulness-based therapy (46)
Cognitive Impairment	TNF inhibitor treatment (74)	

* earlier studies showed conflicting results. ** should only be initiated after an appropriate psychiatric evaluation. TNF = tumor necrosis factor.

Next to fatigue, SFN-related symptoms were reported by the vast majority of patients (86%) in a recent European survey (17). SFN is difficult to diagnose and to treat (13). Patients may experience a myriad of symptoms, but frequently present with neuropathic pain or autonomic dysfunction (76). SFN is usually treated with anticonvulsants, antidepressants, topical anesthetics or opioids (46). However, these standard treatment options are often not effective (13). Retrospective studies showed that intravenous immunoglobulin (IVIg) and tumor necrosis factor (TNF) inhibitors might be effective in reducing SFN-related symptoms (75,76). Furthermore, the erythropoietin agonist cibenitide (ARA290) showed promising results on corneal nerve fiber abundance in a phase 2b clinical trial (82). No statistical differences were found in patient-reported outcomes, probably due to the design of the study (82).

Other common non-organ manifestations of sarcoidosis are psychological problems. Previous studies reported anxiety in up to 33% of patients and depressive symptoms in up to 66% of patients (46,83). In a study which used a comprehensive diagnostic interview, the prevalence of major depressive disorder remained strikingly high, at 25% (62). Most other studies used questionnaires to screen for depressive symptoms (5,84,85). Patients with depression or anxiety tend to have a higher symptom burden and different perception of disease severity (83). Pulmonary rehabilitation may have a beneficial effect on psychological wellbeing (58). Cognitive behavioural therapy also has the potential to improve stress, anxiety and depression in sarcoidosis (63). Furthermore, regular pharmacological therapy for depression and anxiety (antidepressants and anxiolytics) could be offered after an appropriate psychiatric evaluation (63).

Cognitive problems, including memory loss, concentration difficulties and impaired short-term memory are reported by more than 50% of sarcoidosis patients (17,81). At present, the cause of cognitive failure is considered multifactorial, and possibly related to chronic inflammation. Currently, no convincing therapies or interventions are available. An observational study indicated that TNF inhibitor treatment may have a beneficial effect on cognition, as measured by the cognitive failure questionnaire (CFQ) (74). Besides, treatment of associated symptoms may also ameliorate cognitive function.

Comorbidities may also importantly impact QoL and are more prevalent in patients with sarcoidosis compared to the normal population (41,86,87). A higher number of comorbidities is associated with more frequent hospitalizations and a higher mortality rate (87,88). The development of new comorbidities, related

either to steroid use or to sarcoidosis itself, after the diagnosis of sarcoidosis is independently and strongly associated with a number of adverse outcomes, including worse QoL, risk of hospitalization, and financial impacts (4). One study showed that more than half of sarcoidosis patients have more than one comorbidity, with arterial hypertension, thyroid disorders and diabetes mellitus being the most prevalent comorbidities (86). Another study found a significant higher prevalence of chronic liver disease, autoimmune diseases, chronic pulmonary diseases and cancer in patients with sarcoidosis (87). A study in African-American sarcoidosis patients reported that 90% of patients had one or more comorbidities (89). The number of comorbidities is higher in older patients, multi-organ involvement and patients with lower incomes (4,86). Patients with comorbidities obviously have a higher disease complexity, making multidisciplinary management of sarcoidosis even more essential (87). The presence of comorbidities should therefore be carefully (re)assessed during the disease course.

Disease Modifying-Treatment

Not all patients with sarcoidosis require pharmacological treatment, as the majority will have spontaneous regression of the disease (2). Treatment is primarily aimed at suppression of the immune system, and thereby preventing organ damage. The main reasons to start treatment are “to avoid danger or improve quality of life” (90). Factors which should be taken into account are the probability of spontaneous resolution, risk for disease progression, extent of disease, organ dysfunction, activity of sarcoidosis, symptom burden and patient preferences (2,5,12,16).

Pharmacological treatment of pulmonary sarcoidosis should be considered for patients with significant pulmonary symptoms and patients with an impaired or deteriorating lung function (16,91). For extrapulmonary sarcoidosis, the ATS/ERS/WASOG guidelines state that treatment should always be initiated in case of cardiac sarcoidosis, involvement of the central nervous system, hypercalcemia and ocular sarcoidosis not responding to topical treatment (92). Other common indications for treatment are hepatic involvement (impaired liver function, portal hypertension), splenic involvement, bone marrow involvement (cytopenia), nephrolithiasis and skin involvement with disfiguring lesions (16). Treatment may be initiated in patients who have disabling symptoms without organ damage; however, this should always be a shared-decision with patients as medication can have debilitating side effects (12,16). Consequently, efficacy and side effects of treatment should be assessed during every outpatient clinic visit.

The current guideline, dating from 1999, states that “the appropriate treatment has not been well-defined for all patients” (92). Presently, oral corticosteroids (e.g., prednisolone) are recommended as the first-choice therapy for sarcoidosis (92). This recommendation is mainly based on expert opinion and a few relatively small observational studies and low-quality randomized trials from over 20 years ago (91,93). Older studies have demonstrated that corticosteroids lead to an improvement in lung function, especially in patients with initial severe impairment of lung function (94,95). Although corticosteroid treatment leads to short-term improvement of lung function, radiological improvement, and symptom reduction, previous studies have not conclusively demonstrated a beneficial effect in preventing disease progression (16,91). Disease relapse occurs in over 30% of patients after discontinuation of corticosteroids. Furthermore, due to the lack of larger randomized trials the optimal dosage and duration of treatment remains unclear (93).

The most frequently used second-line treatment is the folic acid antagonist methotrexate (96). Methotrexate has a significant steroid-sparing effect and improves lung function (97,98). Methotrexate is increasingly used as first-line agent in case of (relative) contra-indications for corticosteroids (96). A second choice second-line treatment is azathioprine. A retrospective study in the Netherlands and Belgium showed that azathioprine and methotrexate were equally effective, but azathioprine appeared to have more side effects (97). Mycophenolate mofetil and leflunomide are other second-line alternatives (1). Antimalarial medication (chloroquine, hydroxychloroquine) is regularly prescribed in patients with cutaneous involvement or hypercalcemia (99,100).

In refractory sarcoidosis, TNF inhibitors can be prescribed as a third-line agent. Infliximab has been studied in randomized controlled trials and may have beneficial effects on both pulmonary and extra-pulmonary sarcoidosis in a subgroup of carefully selected patients (101–103). Adalimumab also appears to be effective (104). Other treatment options have recently emerged for patients with progressive sarcoidosis. The INBUILD study showed that nintedanib is effective in reducing forced vital capacity decline in patients with fibrotic interstitial lung disease, including sarcoidosis (105). The efficacy of pirfenidone in progressive fibrotic sarcoidosis is also being studied (NCT03260556). Recently, inhibition of the JAK-STAT signaling pathway has been identified as a novel promising treatment target in sarcoidosis; prospective research is ongoing (NCT03910543, NCT03793439) (106). Not only is more research needed for refractory sarcoidosis, but better evidence-based treatment for first-line therapy, aiming at a better

balance between effects and side effects, is also highly needed. A multicenter trial evaluating the efficacy and side effects of prednisone and methotrexate as first-line treatment for pulmonary sarcoidosis has recently started in the Netherlands. A detailed description of medication for sarcoidosis is outside the scope of this review; for an extensive overview, we refer you to other published reviews specifically focusing on this topic (1,2,12,16,90,93).

Extra Pulmonary Specialists

Pulmonary physicians play an important role in the management of sarcoidosis patients, as the lungs are affected in up to 90% of patients. Nevertheless, a multidisciplinary team is needed to improve efficiency of care and outcomes for patients, as many organs can be affected and symptoms are wide-ranging (7,107). While it is quite obvious that other medical specialists contribute their expertise in cases of extra pulmonary sarcoidosis, healthcare providers such as occupational health physicians, pain specialists or specialist nurses should not be forgotten (7,18) (Figure 2). Work participation is lower in patients with sarcoidosis; patients have more health-related sick days and a substantial income loss compared with the normal population (3,4,18,20). Consequently, many patients undergo work capacity assessments and occupational health physicians need to be well-educated about sarcoidosis (13,18). Although the role of specialist nurses is not as established as in other interstitial lung diseases, specialist nurses could function as coordinators of care in sarcoidosis and give patients practical and emotional support. In a small minority of patients, disease will progress despite all treatment lines. In a subgroup of these patients, lung transplantation may be an option. Furthermore, even though mortality is overall low in sarcoidosis, a multidisciplinary approach should also include palliative care specialists in end-stage disease or in case of a high disease burden.

Conclusions

A comprehensive, multidisciplinary approach is essential to treat patients with such a heterogeneous disease as sarcoidosis. Besides aiming at disease modification with pharmacological interventions, patients should also be offered supportive comprehensive care aimed at relieving symptoms and optimizing QoL. Patients' preferences should be guiding all treatment decisions. To allow for better evidence-based treatment in the future, more research into both pharmacological and non-pharmacological treatment options is highly needed.

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The background is an abstract composition of layered, torn paper and watercolor splatters. A large, light brown paper shape occupies the top half, with smaller, darker brown and red splatters scattered around it. In the bottom left, there is a large, vibrant red watercolor shape. In the bottom right, a smaller, darker red shape is visible. The overall effect is artistic and textured.

Part II

IMPROVING PHARMACOLOGICAL
TREATMENT FOR PATIENTS
WITH SARCOIDOSIS



Chapter 3

Comparison of the treatment
guidelines for sarcoidosis:
common sense in the
search of evidence

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Vivienne Kahlmann, Catharina C. Moor,
Jelle R. Miedema, Marlies S. Wijsenbeek

Centre of Excellence for Interstitial Lung Diseases and Sarcoidosis,
Department of Respiratory Medicine, Erasmus MC,
University Medical Center, Rotterdam, the Netherlands

To the Editor:

We congratulate the authors with the highly anticipated European Respiratory Society (ERS) clinical practice guidelines on treatment of sarcoidosis (1). The ERS clinical practice guidelines are an update of the ATS/ERS/WASOG guideline from 1999. The current Task Force Committee has put more emphasis on patient tailored choice than the 1999 guideline. They used the GRADE methodology to develop twelve specific treatment recommendations for management of sarcoidosis. All recommendations were based on very low to low quality of evidence. As such, an important message of the 2021 guideline is that high- or even moderate quality evidence for optimal management of sarcoidosis is lacking (2). Although knowledge of the pathogenesis of sarcoidosis has improved, this has not yet translated into better evidence-based first- and second-line therapies for patients with pulmonary sarcoidosis. For refractory sarcoidosis, third-line therapies such as infliximab and adalimumab have become available. Next to the ERS clinical practice guidelines, the British thoracic society (BTS) recently published a clinical statement on pulmonary sarcoidosis, which covers both diagnosis and management (3). The BTS statement did not use the GRADE methodology to rate the level of evidence; instead, they chose to provide clinical practice points, predominantly based on expert opinion and clinical experience, due to the weak available evidence.

Interestingly, the ERS and BTS documents provide slightly different recommendations, especially regarding medication dosages and treatment schedules (1, 3). The ERS guideline advises to initiate prednisone treatment at a dose of 20mg/day, whereas the BTS statement advises to start with 20-40mg/day. Both ERS guideline and BTS statements suggests addition of methotrexate in patients who have continued disease or unacceptable side effects of glucocorticoids. The ERS guideline advises a dosage of 10-15mg/week and suggests (in the supplement) that there are guidelines underpinning this recommendation, which to our knowledge do not exist. The BTS statement advises to start with a dose of 5-10mg/week and increase until a maintenance dose of 15-20mg/week. No recommendations about duration and tapering of methotrexate treatment are made. To highlight differences and similarities in the existing guidelines and changes from the previous guideline, we have provided an overview of recommendations focused on pulmonary sarcoidosis in **Table 1**.

Table 1: Comparison of the treatment guidelines for pulmonary sarcoidosis*

	ERS guidelines 2021	BTS statement 2020	ATS/ERS/WASOG guideline 1999
Methodology	Task force formulated PICO questions and used the GRADE methodology to rate the level of evidence	Clinical statement group (pulmonologists, nurses, radiologist and patients) provided clinical practice points. The content was developed in accordance with the BTS Standards of Care Committee (SOCC)	Guideline written by sarcoidosis experts. Level of evidence is largely based on expert opinion.
When to start treatment	Patients with major involvement from pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis (strong recommendation, low quality of evidence)	(1) Potential danger of a fatal outcome or permanent disability (2) Unacceptable loss of QoL	• No clear recommendation when to start treatment for pulmonary sarcoidosis • Most health-care providers prescribe corticosteroids in case of progressive symptomatic disease • In asymptomatic patients treatment may be required in case of pulmonary function impairment or persistent pulmonary infiltrates
First-line treatment			
Prednisone	(1) High risk: • Initial treatment 20mg/day. Maintenance dose 5-10mg/day to every other day • Inhaled steroids not advised (2) Intermediate risk, but impaired QoL: 5 to 10 mg/day	(1) Pulmonary sarcoidosis: • Initial treatment 20-40mg/day for 4 to 6 weeks. Slow tapering to maintenance dose of 5-10mg/day • Inhaled steroids not advised (2) Loss of QoL: the choice and dose of agent should be negotiated with the patient	• Initial treatment 20-40mg/day • Evaluation for response after 1-3 months • In responders taper prednisone to 5-10mg/day or every other day • Continue treatment for at least 12 months
Second-line treatment			
General statement	Addition of methotrexate is advised for symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids and have continued disease or unacceptable side effects from glucocorticoids (conditional recommendation, very low quality of evidence) Azathioprine, mycophenolate and leflunomide are also effective in pulmonary sarcoidosis. Chloroquine was mildly beneficial (not assessed per GRADE methodology)	• Review diagnosis and treatment compliance before introducing second-line agents • Indications for second-line therapy: (1) uncontrolled disease or unacceptable symptoms, (2) intolerable side effects, (3) inability to taper prednisone below 10-15mg/day, (4) presents of comorbidities likely related to corticosteroids, (5) strong patient aversion against steroids (can occasionally be used as first-line treatment)	• Cytotoxic agents have been used to treat sarcoidosis • It is not clear when cytotoxic agents should be used • The evidence is based on case reports and small cohort studies • Methotrexate and azathioprine are the preferred agents • Cyclophosphamide should be reserved for refractory cases (high toxicity profile)

Table 1: Continued

	ERS guidelines 2021	BTS statement 2020	ATS/ERS/WASOG guideline 1999
Methotrexate	10-15mg once a week (conditional recommendation, very low quality of evidence)	• Most frequently used • Initiate at 5-10mg per week and increase every two weeks to a target of 15-20mg	10-25mg/week
Azathioprine	50-250mg/day	• Initiate at 50mg/week, increase by 25mg every 2-3 weeks until the maintenance dose is reached (typically 2mg/kg)	50-200mg/day
Mycophenolate mofetil	500-1500mg/ twice a day	• In general: do not consider before MTX and AZA • Usual dose between 1000-1500mg twice a day	Not mentioned
Leflunomide	10-20mg/day	• No advise on treatment dose	Not mentioned
Cyclophosphamide	Not mentioned	Rarely used as second-line treatment due to its toxicity profile	50-150mg/day or 500-2000mg every two weeks intravenously
Hydroxychloroquine/ chloroquine	200-400mg/day	• Mainly advocated for use in fatigue, joint and skin sarcoidosis. Might help reduce prednisone dose in pulmonary sarcoidosis • Usual dose 200mg once or twice/day	200-400mg/day
Third-line treatment			
General statement	Infliximab is advised for symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease (conditional recommendation, very low quality of evidence) Adalimumab was also found to be effective (not assessed per GRADE methodology)	• Biological agents are considered third-line therapeutic agents, to be initiated in pulmonary disease only after failure of second line treatment • Screen for latent tuberculosis infection	• TNF-alpha inhibitors were not available at the time the guideline was published • Agents proposed based on response in selected cases: cyclosporine, melatonin, thalidomide, and pentoxifylline
Infliximab	Initiate at a dose of 3-5mg/kg, second dose two weeks later, than once every 4-6 weeks	• Improves disease control in combination with MTX and AZA • Should initially be given every 2 weeks and then every 4-8 weeks as part of maintenance therapy • No advise on treatment dose	Not mentioned
Adalimumab	• 40mg every 1-2 weeks	Not mentioned	Not mentioned

Table 1: Continued

ERS guidelines 2021		BTS statement 2020	ATS/ERS/WASOG guideline 1999
Continued disease after third-line treatment			
General statement	To consider on a case by case basis (not assessed per GRADE methodology)	Not mentioned	Not mentioned
Rituximab	• Small case series supports the use of rituximab • 500-1000mg every 1-6 months	Not mentioned	Not mentioned
Repository corticotropin injection	• Retrospective studies showed an steroid sparing effect • 40-80 units twice a week	Not mentioned	Not mentioned
JAK inhibitor	• Response reported in small retrospective case series • No advise on treatment dose	Not mentioned	Not mentioned
Antifibrotic therapy			
General statement	Future research: Also the role of anti-fibrotic agents such as nintedanib and pirfenidone need to be further studied	At time of publication pirfenidone and nintedanib were only registered for idiopathic pulmonary fibrosis	Not mentioned

*Recommendations as stated in the guidelines. ERS: European Respiratory Society; BTS: British Thoracic Society; ATS: American Thoracic Society; WASOG: World Association of Sarcoidosis and Other Granulomatous Disorders;

PICO: Patients, Intervention, Comparison, Outcomes; GRADE: Grading of Recommendations Assessment, Development and Evaluation; QoL: qualityof life; MTX: methotrexate; AZA: azathioprine; TNF: tumour necrosis factor.

As shown in the guideline recommendations, evidence for first- and second-line treatment options is still limited. Optimal prednisone treatment schedules are unknown and it remains unclear whether this treatment prevents disease progression in the long-term (4). Most studies in the past decade focused on novel third-line treatment options in patients with refractory pulmonary sarcoidosis, often glucocorticoid dependent and several studies are ongoing (5). Some clinical studies based on a strong pathophysiological rationale showed disappointing results (6). This could be due to several reasons. The heterogeneity of sarcoidosis and variable disease course make a good study design challenging, particularly regarding patient selection and relevant outcome measures. Studies focusing on patients with refractory sarcoidosis are biased, as those patients may have a distinct immunological profile compared to treatment-naïve patients and could respond different to medication (7, 8). Choosing relevant endpoints in sarcoidosis remains challenging as disease phase, amount of irreversible lung disease, variable physiological impairment (obstructive and restrictive) and differences in burden of disease should be taken into account to capture a meaningful treatment effect. Therefore, studies with new agents should ideally be performed in an unbiased cohort of treatment-naïve patients with sarcoidosis.

We believe that more studies should focus on better evidence-based first- and second-line treatment. First of all, better insights should be obtained on the effect of treatment on the natural course of sarcoidosis. Currently, it is often not clear which patients with pulmonary sarcoidosis we should treat. In the guideline from 1999 no recommendation was provided on when to start treatment, whereas the recent guideline mainly gives general recommendations (treatment is advised in patients with pulmonary involvement at risk of mortality or permanent disability). Secondly, as prednisone is often accompanied by side effects and reduced quality of life, research into other first-line treatment options is needed. Recently, an observational study found that first-line treatment with methotrexate seems to have the same efficacy as prednisone (9). A randomized controlled trial investigating the efficacy of methotrexate compared with prednisone as first-line treatment option for pulmonary sarcoidosis is currently ongoing (10). This study combines clinical and fundamental research, which will hopefully provide new insights into the pathophysiology of sarcoidosis and the immunological profile of responders versus non-responders on treatment. Finally, optimal treatment schedules for first- and second-line treatment should be established, to avoid “under treatment” with the risk of organ damage and

“over treatment” with the risk of debilitating or dangerous side effects. At this moment an ongoing trial evaluates the efficacy and safety of prednisone 40mg/day versus prednisone 20mg/day in sarcoidosis (NCT03265405).

Hopefully, the new guidelines will not only stimulate patient engagement and common sense when making treatment decisions, but will also encourage the field to generate high-quality evidence to support those decisions.

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Chapter 4

Patient-reported side effects of prednisone and methotrexate in a real-world sarcoidosis population

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Vivienne Kahlmann^{1*}, Catharina C. Moor^{1*}, Marcel Veltkamp^{2,3}
and Marlies S. Wijsenbeek¹

1. Centre of Excellence for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
2. ILD Center of Excellence, Department of Pulmonology, St. Antonius Hospital, Nieuwegein, The Netherlands
3. Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, The Netherlands

*These authors share first authorship.

Abstract

Currently prednisone is the first-line pharmacological treatment option for pulmonary sarcoidosis. Methotrexate is used as second-line therapy and seems to have fewer side effects. No prospective comparative studies of first-line treatment with methotrexate exist. In this study, we evaluated patient-reported presence and bothersomeness of side effects of prednisone and methotrexate in a sarcoidosis population to guide the design of a larger prospective study. During a yearly patient information meeting 67 patients completed a questionnaire on medication use; 11 patients never used prednisone or methotrexate and were excluded from further analysis. Of the remaining 56 patients, 89% used prednisone and 70% methotrexate (present or former). Significantly more side effects were reported for prednisone than for methotrexate, 78% versus 49% ($p = 0.006$). In conclusion, methotrexate seems to have fewer and less bothersome side effects than prednisone. These findings need to be confirmed in a prospective study.

Background

Sarcoidosis is a granulomatous disease with a heterogeneous presentation. The lungs are involved in over 75% of patients (1). The decision to start treatment depends on different factors, such as the threat to organ function and symptom severity. Treatment aims at improving organ function, as well as quality of life (QoL) (2). Prednisone is currently the first-line pharmacological treatment option in pulmonary sarcoidosis. Prednisone leads to short-term improvement of pulmonary function and symptoms (3). However, prednisone often has major side effects, such as weight gain, depression, osteoporosis and diabetes, which may lead to impaired QoL (4–6). Hence, patients and doctors report an urgent need for better treatment options. Methotrexate is presently considered second-line therapy and has not been studied as first-line treatment (3,7). Methotrexate may have fewer side effects than prednisone. Although the side effects of prednisone and methotrexate are well known, they have never been compared in patients with sarcoidosis. In this survey, we evaluated patient-reported side effects of prednisone and methotrexate in a real-world sarcoidosis population.

Methods

During a yearly sarcoidosis patient information meeting at the Erasmus University Medical Center in 2019, patients were invited to complete a 14-item survey on medication use and experiences with prednisone and methotrexate. Patients with confirmed sarcoidosis, treated in the Erasmus Medical Center, were invited by letter to attend the meeting. All patients, who were attending the meeting, were invited to participate. Patients provided informed consent to use the survey data, and could provide additional consent to retrieve information from their medical records. The survey consisted of open-ended questions (**Supplementary File 1**). If patients used combination therapy and experienced side effects, they reported to which medication they believed the side effects belonged. Bothersomeness of side effects was reported on a scale from 0 (not bothersome at all) to 10 (very bothersome). This study was approved by the Medical Ethics Committee of the Erasmus Medical Center. The chi-square test was used to evaluate between-group differences in the reported side effects. The Mann–Whitney U test was used to compare the number and bothersomeness of side-effects. Data were analyzed in SPSS version 25.0.

Results

In total, 67 patients completed the questionnaire, 11 patients never used prednisone or methotrexate and were excluded from further analysis. Of the remaining 56 patients, 89% used prednisone, 70% methotrexate and 21% also used other medication (present or former). Mean age was 53 years (SD 9.8) and 57% were female. Of the 41 patients that gave consent to use their clinical data; 98% had hilar or mediastinal lymphadenopathy, 80% had pulmonary involvement, 17% had cardiac involvement, 12% had ocular sarcoidosis, 12% had skin manifestations, 12% had neurological involvement, 5% had bone involvement, 5% had sarcoidosis in the liver, and 5% had renal involvement. Median time after diagnosis was 4 years (IQR 2.2–6.8), median time on medication was 24 months (IQR 6.0–36.0) for prednisone and 12 months (IQR 6.0–24.0) for methotrexate.

Of the 50 patients using prednisone, 78% reported one or more side effects. Patients most frequently reported weight gain (48%), psychological problems/behaviour change (24%), sleep problems/fatigue (20%); results are shown in **Figure 1**. Median bothersomeness of side effects ($n = 20$) was 6.0 (IQR 5.0–8.0) and average number of side effects ($n = 39$) were 2.0 (IQR 1.0–3.0). In the 39 patients treated with methotrexate, fewer side effects were reported: 49% reported one or more side effects such as nausea or other gastrointestinal complaints (31%), general malaise (10%), headache (5%), liver test abnormalities (5%) and hair loss (5%). Median bothersomeness of side effects ($n = 10$) was 4.5 (IQR 3.8–6.2), and average number of side effects ($n = 19$) were 1.0 (IQR 1.0–2.0).

Significantly more patients with prednisone had side-effects compared with methotrexate ($p = 0.006$). Moreover, patients with prednisone reported a higher number of side effects ($p = 0.012$) and more bothersome side effects ($p = 0.044$); results are shown in **Figure 2**.

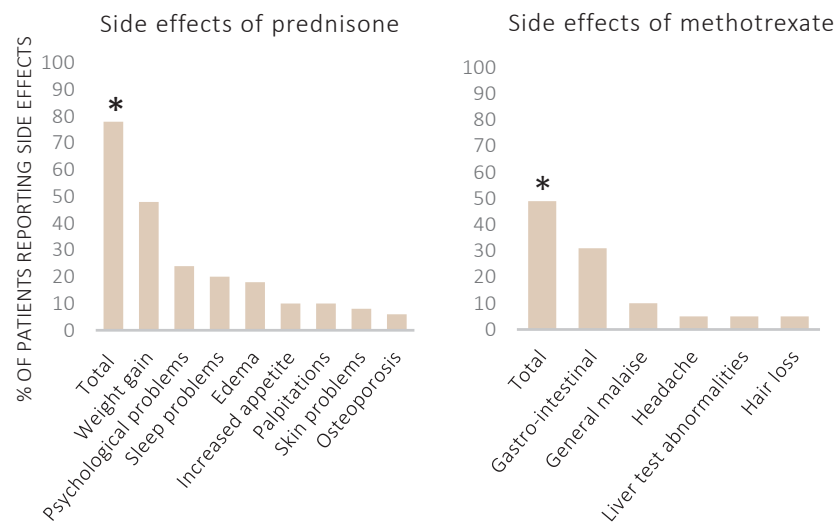


Figure 1. Side effects reported by 50 patients treated with prednisone and 39 patients treated with methotrexate.

'Total' indicates one or more reported side effects. * The number of patients who reported side effects were significantly higher for prednisone ($p = 0.006$).

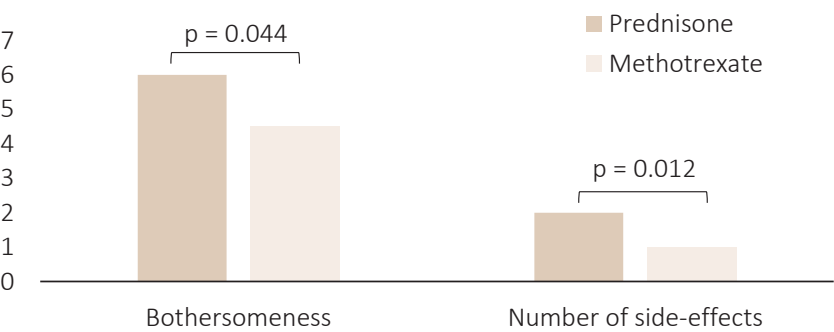


Figure 2. Average number and bothersomeness (on a scale from 0–10) of side effects of prednisone and methotrexate.

Of the 39 patients who experienced side effects of prednisone, 20 reported bothersomeness of side effects. Of the 19 patients who experienced side effects of methotrexate, 10 reported bothersomeness of side-effect.

Discussion

This study compared patient-reported side effects of prednisone and methotrexate in a real-world sarcoidosis population. Importantly, patients reported significantly fewer and less bothersome side effects with methotrexate than with prednisone.

Prednisone is the cornerstone of pharmacological treatment for pulmonary sarcoidosis. Awareness of the potential debilitating side effects of prednisone and impact on QoL in patients with sarcoidosis has increased (4). Hence, the need for steroid-sparing alternatives is mentioned in the most recent consensus statement on treatment of sarcoidosis (3). Unfortunately, research into alternative treatment options is scarce. This survey was conducted to explore the rationale for a randomized controlled trial comparing the efficacy and tolerability of methotrexate and prednisone as first-line treatment for sarcoidosis (8).

Findings of this study indicate that methotrexate seems to have fewer side effects than prednisone in clinical practice. One of the limitations of this study was that the open-ended questions rely on patients' recollection. Although recall bias might have had an effect on the reported side effects, we expect this would be similar in both groups. Furthermore, we focused on patient experiences and therefore information on physician reported side effects is lacking. As this was a retrospective single-center study, results need to be confirmed in a larger prospective cohort (8).

In conclusion, the results of this current study reveal the patient perception on prednisone and methotrexate use and emphasize that better evidence-based treatment options with fewer side effects are highly needed to improve QoL for patients with sarcoidosis.

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Supplementary appendix

SURVEY ABOUT MEDICATION USE – SARCOIDOSIS PATIENTDAY

Age: years Gender: male/female

When was the diagnosis sarcoidosis confirmed? (Example: March 2014)
.....

Are you currently using medication for sarcoidosis? Yes/No

If yes, what medication do you use and in what dosage?
.....

For how long have you been using the above mentioned medication?
.....

Have you experienced any side effects of your sarcoidosis medication? Yes/No

Side-effect	Medication?	Bothersomeness of side effects (Not bothersome = 0, very bothersome = 10)
.....		
.....		
.....		
.....		

Please fill in the next three questions if you have used prednisone in the past

Did you experience side effects of prednisone?

If yes, please describe the most important side effects.

.....

Why did you stop taking prednisone? (example: side effects, prednisone was not effective)

.....

How long did you use prednisone?

.....

Please fill in the next three questions if you have used methotrexate in the past

Did you experience side effects of methotrexate? If yes, please describe the most important side effects.

.....

Why did you stop taking methotrexate? (example: side effects, methotrexate was not effective)

.....

How long did you use methotrexate?

.....

Chapter 5

COVID-19 infection in patients with sarcoidosis: susceptibility and clinical outcomes

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Vivienne Kahlmann,MD^{1*}, Michael Manansala,MD^{2*}, Catharina C. Moor, MD-PhD¹, Shiva Shahrara PhD^{3,4}, Marlies S. Wijsenbeek, MD-PhD¹, Nadera Sweiss, MD³

1. Centre of Excellence for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
2. Department of Medicine, Academic Internal Medicine, University of Illinois at Chicago, Chicago, Illinois.
3. Division of Rheumatology, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA.
4. Jesse Brown VA Medical Center, Chicago, Illinois, USA

*These authors share first authorship

Abstract

Purpose of review

Patients with sarcoidosis may be at higher risk of coronavirus disease 2019 (COVID-19) as over 90% of the patients have pulmonary involvement and many are treated with immunosuppressive agents. This review will summarize the current literature regarding sarcoidosis and COVID-19, with a particular focus on susceptibility, clinical outcomes, management, and approach to vaccination.

Recent findings

Data about COVID-19 and sarcoidosis include a number of case series and reports, cohort studies, and registries. Literature is not conclusive whether patients with sarcoidosis have increased susceptibility to COVID-19. Patients with moderate to severe impaired pulmonary function may be at increased risk of adverse outcomes and mortality. Whether immunosuppressive medication increases risk of COVID-19 severity or affects vaccination response is not yet clear. Novel approaches, such as telemedicine and home monitoring programs, are promising to ensure continuity of care for patients with sarcoidosis during the COVID-19 pandemic.

Summary

Current evidence about the risk and clinical outcomes of COVID-19 infection in patients with sarcoidosis is mainly extrapolated from other immune-mediated diseases. Hence, further research that focuses on the sarcoidosis population is warranted.

Keywords

COVID-19, sarcoidosis, management, immunosuppression, vaccination

Introduction

Sarcoidosis is a systemic inflammatory disease, caused by an unidentified trigger, leading to an inflammatory response, cytokine release and granuloma formation (1). These granulomas are commonly found in the lungs, with 90% of patients having pulmonary manifestations of disease(1,2). Patients with sarcoidosis may be at higher risk of contracting coronavirus disease 2019 (COVID-19) and worse clinical outcomes due to pulmonary involvement, comorbidities, and the use of immunosuppressive medication. In this review, we strive to answer clinical questions to provide guidance to improve care for patients with sarcoidosis during the COVID-19 pandemic. We will discuss susceptibility and risk of adverse COVID-19 outcomes in patients with sarcoidosis, with a particular focus on immunosuppressive therapy. Subsequently, we will elaborate on the management and optimal monitoring of patients with sarcoidosis during the COVID-19 pandemic. Finally, we will touch on the management of COVID-19 as well as approach to vaccination in patients with sarcoidosis.

Key points

- There is limited data currently available to determine if patients with sarcoidosis are at increased risk of contracting COVID-19
- Patients with sarcoidosis with impaired pulmonary function may be at increased risk of adverse COVID-19 outcomes
- Rituximab may increase risk of COVID-19 severity, although there is no conclusive evidence whether other immunosuppressive medications have a similar effect
- Home monitoring programs can be useful to maintain the usual standard of care during the COVID-19 pandemic, and to monitor patients with sarcoidosis and COVID-19 in the outpatient setting
- It is recommended to offer COVID-19 vaccination to patients with sarcoidosis; the ACR offers guidance regarding approach to COVID-19 vaccination and the use of immunosuppressive medication

Are there similar cellular pathways in the immune response in COVID and sarcoidosis?

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 enters the cell by binding to the angiotensin converting enzyme 2 (ACE-2) receptor in the nasopharynx, oropharynx and lungs, leading

to a viral inflammatory response (3). The majority of patients who develop COVID-19 experience mild to moderate symptoms, while a small subset of patients experience severe manifestations of disease such as acute respiratory distress syndrome and multiorgan failure. The latter is thought to be due to an unattenuated hyperinflammatory response, a phenomenon known as cytokine storm syndrome (4). The inflammatory cascade begins with viral RNA binding to pattern recognition receptors (PRR) as the virus enters a cell of the innate immune system. Upon activation of these receptors, a series of events triggers the secretion of pro-inflammatory cytokines including tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-1, IL-18, but most importantly interferon (IFN). This flood of cytokines can induce effector T-cell responses as well as recruit other immune cells to propagate further inflammation. Treatment for severe COVID-19 aims to target steps in this inflammatory cascade (5).

Sarcoidosis is thought to be caused by exposure to an unidentified antigen which leads to an inflammatory response in predisposed individuals. Contact with an antigen activates T lymphocytes, macrophages and antigen presenting dendritic cells and leads to release of pro-inflammatory cytokines(1). These pro-inflammatory cytokines play an important role in T-cell differentiation. While sarcoidosis was once considered a typical Th1 disease with several Th1 cytokines found in bronchoalveolar lavage fluid cells, recently, Th17 and Th17.1 cells were found to correlate with prognosis (6,7). Several of the cytokines involved in T-cell proliferation and differentiation signal through the Janus Kinase (JAK)-signal transducer and activator of transcription (STAT) pathway (1). Other important cytokines contributing to granuloma formation and maintenance are IFN-gamma and TNF-alpha (1).

There may be some similarities in the pathogenesis of COVID and sarcoidosis. First of all, there is some overlap in cytokines involved, such as IL-6, IL-18 and TNF-alpha. Similarly, the JAK-STAT pathway is an important mediator in the immune response in sarcoidosis as well as in COVID-19 (1,5). Interestingly, inhibition of the JAK-STAT pathway has been proposed as therapy for both refractory sarcoidosis and severe COVID-19 (8-10). Whether potential similarities in pathogenesis of the two diseases leads to an increased – or decreased – risk of severe COVID-19 infection in patients with sarcoidosis requires further study.

Is there an increased susceptibility of COVID-19 in patients with sarcoidosis?

Although our understanding of the pathophysiology of COVID-19 has vastly improved since the start of the pandemic, little is still known regarding how sarcoidosis impacts susceptibility to COVID-19 infection. Patients with sarcoidosis

may have lymphopenia and suppression of the peripheral immune response at baseline, increasing susceptibility to infection (11). Additionally, the use of immunosuppressive medication increases the risk of opportunistic infections, but whether this also applies to COVID-19 needs to be elucidated (12). Baughman et al. conducted a survey study in 5200 patients with sarcoidosis, of whom 116 patients reported COVID-19 infection and 18 required hospitalization (13). The rate of COVID-19 in this cohort was 2.23% or 22,308 cases per million from April to July 2020. This was notably higher than the rate of COVID-19 in the general US population, which was 1,060 cases per million during the same time period. However, a subgroup analysis comparing patients with sarcoidosis to patients without sarcoidosis in the same geographic area found that rates of infection were similar between both groups. In the same study, the presence of pulmonary sarcoidosis and neurosarcoidosis were identified as factors that increased risk of COVID-19. Also, rituximab was associated with an increased risk of contracting COVID-19, while other immunosuppressive therapy was not. Interestingly, the presence of diabetes, hypertension, heart disease, or chronic obstructive pulmonary disease (COPD) were not associated with increased risk of COVID-19 in this cohort. However, the authors rightly remark that the study was underpowered to detect small but significant changes due to low number of cases of COVID-19 in the cohort. At this point in time, it is unclear whether patients with sarcoidosis are at increased risk of COVID-19.

Is there increased risk for severe disease or poor outcomes of COVID-19 in patients with sarcoidosis?

There are several factors that may increase the risk of adverse COVID-19 outcomes in sarcoidosis, which we define in this review as intubation or in-hospital mortality. Sarcoidosis affects the lung in most patients and can result in diminished pulmonary reserve in the form of obstructive or restrictive lung disease(2,14). Multiple meta-analyses have found that respiratory diseases, especially COPD, are associated with increased risk of severe COVID-19 (15,16). Several studies have shown that patients with interstitial lung disease (ILD) who contract COVID-19 were more likely to require hospital admission or ICU level care and had increased mortality rates, especially those with pulmonary fibrosis(17-19). Indeed, Morgenthau et al. found that the presence of moderately to severely decreased pulmonary function in patients with sarcoidosis is associated with increased rate of adverse COVID-19 outcomes(20). Additionally, comorbid conditions, such as hypertension and diabetes mellitus, that have been shown to be independently associated with increased mortality in COVID-19 are commonly seen in patients with sarcoidosis (15,16,21). Overall, the current literature suggests that patients

with sarcoidosis who contract COVID-19 may be at risk for worse outcomes. This highlights the need for close monitoring of patients with sarcoidosis and COVID-19. However, larger cohort studies are required to further characterize and quantify rates of severe COVID-19 outcomes in this population.

Do immunosuppressive medications influence the disease course of COVID-19?

In general, immunosuppressive medications, especially glucocorticoids, increase the susceptibility to opportunistic infections (22,23). This raises the question whether sarcoidosis patients treated with immunosuppressive medication are at higher risk of COVID-19 compared to patients not using such therapy. As data regarding clinical outcomes of COVID-19 in patients with sarcoidosis on immunosuppressive medication is scarce, we extrapolate outcomes from patients with other inflammatory rheumatic diseases. **Table 1** highlights studies in which clinical outcomes of patients on immunosuppressive therapy are described. Of note, these are all retrospective studies, which prevents conclusions about causal relationships.

The most frequently used medication for sarcoidosis is prednisone. Patients taking less than 10mg prednisone a day do not seem to be at higher risk for hospitalization or death from COVID-19 (24-25). Data are conflicting, however, regarding whether moderate to high dose glucocorticoids (equal to >10mg prednisone/day) is associated with more severe outcomes. Two smaller retrospective studies did not find an association between prednisone >10mg/day and an increased risk of hospitalization and mortality due to COVID-19. However, these studies may have been underpowered to detect small but significant effects (13,17). Two large retrospective studies that used data from the "COVID-19 Global Rheumatology Alliance Provider Registries (C19-GRA)" did demonstrate an association between prednisone >10mg/day and higher risk of hospitalization and death from COVID-19 infection (25,26). As it stands, it is debatable whether moderate to high dose glucocorticoids are an independent risk factor for worse COVID-19 outcomes. Moderate to high dose prednisone is mainly prescribed in cases of severe sarcoidosis, suggesting the adverse outcomes might well be a reflection of sarcoidosis severity and activity. Remarkably, in the Recovery Trial (Randomized Evaluation of COVID-19 Therapy) dexamethasone decreased mortality among COVID-19 patients on oxygen or invasive mechanical ventilation (27). Consequently, dexamethasone is advised for all patients with COVID-19 requiring additional respiratory support, including those with sarcoidosis (28). Other disease modifying anti-sarcoid drugs (DMASD) are methotrexate, azathioprine, mycophenolate and leflunomide. For

these DMASDs, no conclusions can be drawn with regard to the risk of severe COVID-19 due to limited data (13,25,26,29). Interestingly, in an earlier analysis of the C19-GRA, Gianfrancesco and colleagues found that the use of anti-TNF treatment was associated with a lower risk of hospitalization (26,30). It was speculated that this might be related to positive effect of anti-TNF treatment during the inflammatory phase of COVID-19 infection. In a later analysis of the C19-GRA which included a larger cohort of patients, Strangfeld et al. did not find a positive effect of anti-TNF on mortality. Studies on B-cell therapy show that rituximab use was associated with more severe COVID-19 outcomes (25,31). It is suggested that this could be related to B-cell depletion, which can potentially compromise antiviral immunity and development of SARS-CoV-2 antibodies (32). This association, however, may also be influenced by the usual co-administration of methylprednisolone with rituximab (25). Overall, rituximab seems to increase the risk of severe COVID-19, while there is no conclusive evidence whether other immunosuppressive medications increase risk of COVID-19 severity.

How should sarcoidosis be managed during the COVID-19 pandemic?

Early in the COVID-19 pandemic and in the absence of specific data, clinical recommendations on the use of immunosuppressive medication in sarcoidosis were provided. These advised to adjust treatments by prescribing immunosuppressive medication with caution, minimizing dosages or prolonging intervals between dosages if the clinical situation permitted (33). One year later, there still is no conclusive evidence whether immunosuppressive medication increases COVID-19 severity. In general, the European League Against Rheumatism (EULAR) recommends no medication adjustments for patients with sarcoidosis during the COVID-19 pandemic (28). Since sarcoidosis is a heterogeneous disease, treatment regimens are often personalized for individual patients. It is essential to frequently assess the risk-benefit ratio of immunosuppressive medication, especially during the COVID-19 pandemic. The potential benefits of treatment with immunosuppressive medication should be weighed against the risk of undertreatment and subsequent organ damage, while considering the risks and side effects of medication. Notably, uncontrolled inflammatory or autoimmune disease has been associated with increased COVID-19 mortality, which highlights the importance of adequate disease control (25).

Table 1: Immunosuppressive therapy and outcomes of COVID-19 infection in patients with sarcoidosis, interstitial lung disease and rheumatic diseases

Author	Design	Number of patients	Immunosuppressive therapy	Outcome
Baughman, et al, 2020¹³	Self-reporting questionnaire on the risk and outcome of COVID-19 infection in patients with sarcoidosis	5200 patients with sarcoidosis • 116 patients reporting COVID-19 infection • 18 required hospitalization	Data available of 105 patients of the 116 COVID positive patients • Prednisone < 10mg (n=57) • Prednisone > 10mg (n=15) • DMARDS: Methotrexate, azathioprine, mycophenolate, leflunomide (n=24) • Hydroxychloroquine (n=8) • Anti-TNF: infliximab, adalimumab (n=7) • Rituximab (n=7)	• Incidence of COVID-19 was 2.23% • 15.8% of the patients with COVID-19 required hospitalization • Pulmonary sarcoidosis, neurosarcoidosis and rituximab were associated with increased risk of contracting COVID-19 infection • Immunosuppressive therapy was not associated with increased risk of hospitalization
Morgenthau, et al, 2020²⁰	Retrospective cohort study	7337 patients with COVID-19 infection • 37 patients with sarcoidosis	Data available of 37 patients with sarcoidosis and COVID-19 infections • Glucocorticoids (n =11) • Non-Steroid Systemic Anti-Inflammatory Medications: Methotrexate, Azathioprine, Mycophenolate, Infliximab, Hydroxychloroquine (n=14) • No therapy (n=18)	• No significant association between sarcoidosis and adverse outcome (intubation/mechanical ventilation/ mortality compared to the entire cohort) • Risk on adverse outcome was increased in patients with moderate/severe impairment in pulmonary function (OR = 7.8)
Jeny, et al, 2020³³	Retrospective cohort study in 15 French centers	36 patients with sarcoidosis admitted with COVID-19 infection	Data available of 36 patients with sarcoidosis admitted with COVID-19 • Glucocorticoids (n=25) • Methotrexate (n=8) • Mycophenolate (n=3) • Azathioprine (n=3) • Anti-TNF (n=6)	• 36% of the admitted patients required intensive care support • Mortality rate was 14% • High prevalence of chronic comorbidities in the study cohort (33% diabetes, 39% hypertension, 33% lung fibrosis)
Galley, et al, 2020¹⁹	Retrospective cohort study	123 ILD patients with COVID-19 infection • 16 patients with sarcoidosis	Data available of 123 ILD patients with COVID-19 • Glucocorticoids (n=47) • Immunosuppressive drugs (n=45) • No immunosuppressive medication (n=31)	Prednisone and immunosuppressive therapy were not associated with an increased mortality rate

Table 1: Continued

Author	Design	Number of patients	Immunosuppressive therapy	Outcome
Giafrancesco, et al, 2020²⁶	COVID-19 Global Rheumatology Alliance physician-reported registry	600 individuals with rheumatic disease and COVID-19 • 10 patients with sarcoidosis	Data available of 600 patients with rheumatic disease and COVID-19 • Prednisone 1-9mg/day (n= 125) • Prednisone >10mg/day (n=64) • No corticosteroids (n=403) • csDMARD only, including antimalarial therapy (n=272) • b/tsDMARDs only (n=107)	• Prednisone 1-9mg/day was not associated with an increased risk of hospitalization • Prednisone $\geq$ 10mg/day was associated with higher risk of hospitalization compared to no prednisone use (OR=2.05) • Other immunosuppressive medications were not associated with an increase the risk of hospitalization (OR = 1.23, p = 0.48) • Anti-TNF was associated with lower odds (OR = 0.4) of hospitalization compared to no Anti-TNF
Drake, et al, 2020¹⁷	International multicenter audit of patients with ILD admitted with COVID-19	161 ILD patients with COVID-19 infection matched with 322 non-ILD patients with COVID-19 infection • 9 patients with sarcoidosis	Data available of 161 ILD patients with COVID-19 • Methotrexate/azathioprine (n=5) • Mycophenolate (n=17) • Corticosteroids (n=45) • No immunosuppressive therapy or antifibrotic medication (n=106)	• Mortality ILD cohort 49% compared to matched cohort 35% without ILD • Mortality 50% in ILD cohort (n=106) without medication • Mortality 51% in patients with prednisone (n=45) • Patients with impaired lung function and obesity had an increased risk of death from COVID-19
Esposito, et al, 20¹⁸	Case-control study	46 ILD patients with COVID-19 were matched with 92 non-ILD patients • number of patients with sarcoidosis unknown	Data available of 46 ILD patients with COVID-19 • Corticosteroids (n=11) • Other immunosuppression (n=18) • No treatment (n=17)	• Increased mortality in patients with ILD (OR 4.3) • Chronic corticosteroids or other immunosuppressive therapy use was not associated with death.

Table 1: Continued

Author	Design	Number of patients	Immunosuppressive therapy	Outcome
Strangfeld, et al, 2021 ²⁵	COVID-19 Global Rheumatology Alliance physician-reported registry	3729 individuals with rheumatic disease and COVID-19 number of patients with sarcoidosis unknown	Data available of 3729 patient with rheumatic diseases and COVID-19* - Corticosteroids 1-10mg/dag (n=983) - Cotricosteroids >10mg/dag (n=220) - csDMARDS monotherapy (n=651), combination therapy (n=753) - mmunosuppressive (azathioprine, cyclophosphamide, ciclosporin, mycophenolate or tacrolimus) monotherapy (n=175), combination therapy (n=168) - bDMARDS monotherapy (n=723), combination therapy (n=608) - Anti-TNF monotherapy (n=447), combination therapy (n=357) - Rituximab monotherapy (n=91), combination therapy (n=102)	- Prednisone >10mg/day was associated with increased mortality (OR = 1.69) compared with no prednisone use - Rituximab, sulfasalazine, and immunosuppressive therapy were associated with increased mortality compared with methotrexate monotherapy - Chronic lung disease and moderate- to high disease activity were associated with increased mortality

Abbreviations: DMARDS = Disease-modifying antirheumatic drugs, csDMARDS = conventional synthetic DMARDS, bDMARDS = biological DMARDS, tsDMARDS = targeted synthetic DMARDS,

Anti-TNF = anti-tumor necrosis fact. *Data is shown of selected number of immunosuppressive agents, that are frequently used as treatment for sarcoidosis.

How should we treat COVID-19 in patients with sarcoidosis?

Since the beginning of the pandemic, there have been a number of case series and reports that have sought to describe the clinical courses and treatment of COVID-19 in sarcoidosis patients. The literature reveals seven case series and reports, which include a total of 46 sarcoidosis patients who contracted COVID-19 (34-40). Management of COVID-19 in these cases varied and consisted of treatments which are currently not recommended for treatment of COVID-19, such as various antivirals and antimalarials. Given the small number of cases and the heterogeneity of treatments, it is difficult to draw conclusions from the current literature on the optimal management of COVID-19 in specifically in sarcoidosis. In the United States, the current treatment in the general population requiring hospitalization and supplemental oxygen are dexamethasone with or without the antiviral agent remdesivir (41). On the other hand, the European Respiratory Society advises against the use of remdesivir in hospitalized patients and recommends only dexamethasone and tocilizumab in addition to supportive management (42). While these guidelines are also used for sarcoidosis patients, an additional consideration that must be made is continuation or modification of immunosuppressive regimens. The EULAR

guidelines advise to continue chronic corticosteroids during COVID-19 infection (28). The decision to continue or withdraw other chronic immunosuppressive medication during acute COVID-19 requires an assessment of the risk-benefit ratio and should be individualized with each patient. Fortunately, the vast majority of patients with sarcoidosis and COVID-19 will not require hospital admission and supplemental oxygen and can be managed with self-monitoring at home.

How to monitor sarcoidosis patients during the COVID-19 pandemic?
The COVID-19 pandemic has limited access to the hospital and threatened the continuity of care within our healthcare systems. Many follow-up visits are now conducted via telephone or video consultation. This may lead to suboptimal discussions, outcome assessment, and potential delays in treatment decisions. Innovative approaches in daily care, such as home monitoring programs including home spirometry have increasingly been used in the past year (43,44). Portable electronic spirometers have proved to accurately measure forced vital capacity (FVC) at home in patients with interstitial lung disease (45,46). Home spirometry may allow for early detection of deterioration of lung function and guide treatment

decisions (6). Measurement of diffusion capacity is more challenging, but surrogate measures are currently being explored. Recent data suggest a one-minute sit-to-stand test may give an indication of gas exchange impairment and diffusion capacity, but this is not yet validated (47). Virtual platforms also enable collection of patient-reported comorbidities, symptoms, and side effects of medication as well as capturing self-measured data by patients, including blood glucose, blood pressure, and weight. Thus, these novel approaches can be useful to maintain the usual standard of care and continue clinical research for patients with sarcoidosis during and beyond the COVID-19 pandemic (48). Furthermore, home monitoring may improve patient insight into their disease while at the same time empowering patient education and self-management. Home monitoring can also be of great value to closely monitor patients with COVID-19 infection in the outpatient setting, especially for patients with underlying chronic diseases that are at risk for severe COVID-19 disease. Several home monitoring programs for COVID-19 patients have been developed. These programs have demonstrated safety and efficacy in detecting worsening of symptoms while maintaining high patient satisfaction (49-52). A pilot study demonstrated that home monitoring reduced mean duration of hospitalization, especially in patients requiring oxygen support at discharge while being cost-effective (52). Overall, if available, we recommend the use of home monitoring, self-reporting of symptoms and oxygen saturation in patients with sarcoidosis and COVID-19 infection.

What do we know about the vaccination response in sarcoidosis?

Currently, there are no data about COVID-19 vaccination in patients with sarcoidosis. Previous data regarding vaccination in sarcoidosis is limited and conflicting. Seyhan et al. conducted a small case control trial in which the tetanus vaccine was administered to 48 sarcoidosis patients and 33 healthy controls. They found that 50% of the sarcoidosis patients, compared to 23% of healthy controls, did not mount an adequate antibody response to vaccination (53). On the other hand, in another case-control trial, Tavana et al. showed that flu vaccination is safe in sarcoidosis and that sarcoidosis patients mounted an adequate antibody response to vaccination compared to healthy controls (54). Both aforementioned studies, however, are limited by small sample sizes and fail to account for concurrent use of immunosuppression.

As immunosuppressive medications are the mainstay of treatment for sarcoidosis, it is important to consider how these agents will impact the response to vaccination. Although there is a paucity of data in sarcoidosis, this issue has been studied in rheumatoid arthritis (RA). Immunogenicity of the flu vaccine

has been shown to be adequate in RA patients on glucocorticoids (55,56). On the other hand, a study of Fisher et al, showed insufficient antibody response in patients using prednisone doses higher than 10mg a day (57). Studies have shown that methotrexate and TNF-alpha inhibitors may dampen the immunogenicity of the influenza vaccination compared to healthy controls, RA patients still produced adequate levels of antibodies (55-58). Conversely, RA patients on B-cell depleting therapy demonstrate a decreased antibody response to influenza vaccination (58-60), although this effect may be mitigated by administering the vaccine at least 6 months after the last dose of therapy (60,61). In summary, data in RA demonstrates that some agents diminish production of antibodies after vaccination, the relationship between antibody titers and protection from infection is not straightforward as other factors may be more important, such as efficacy of neutralizing antibodies, in determining protection from infection. Vaccination of sarcoidosis patients against COVID-19 is currently recommended (62,63). The American College of Rheumatology (ACR) has provided guidance related to the use of immunosuppressive medications during COVID-19 vaccination (63). Soy et al. prepared a practical approach to the use of immunosuppressive medications during COVID-19 vaccination in rheumatic diseases (64). **Table 2** shows the recommendations of the ACR and of Soy et al.

A recent study investigated the immunogenicity of COVID-19 vaccination in patients with immune-mediated inflammatory diseases (IMID) in two independent cohorts (65). The first cohort consisted of 51 patients with IMID, 25 patients were using methotrexate and 26 patients were using anticytokine and/or other immunomodulators. These patients were compared with 26 healthy controls. The second cohort consisted of 182 healthy individuals, 20 patients with IMID on methotrexate monotherapy and 11 patients treated with TNF alpha inhibitors. In both cohorts, immunogenicity was decreased in patients with IMID who were using methotrexate therapy. Combined analyses showed adequate response in over 90% of the healthy subjects and patients with IMID on biological treatment and only in 62.2% of the patients with IMID on methotrexate. Further studies are needed to confirm this finding and to evaluate if additional doses of vaccine or modification of methotrexate treatment is needed (65).

Table 2. Recommendation on the use of immunosuppressive medication during COVID-19 vaccination in rheumatic disease*

	ACR, 2021 (63)	Soy et al, 2021 (64)
Prednisone	Low dose prednisone (<20mg/day): do not delay vaccination. High dose prednisone (>20mg/day): no consensus was reached.	COVID-19 vaccination should be given in patients receiving prednisone <10mg/day.
Methotrexate	Do not delay vaccination. Skip 1 dose of methotrexate after vaccination.	In stable patient skip 1 dose of methotrexate before and 1 dose after vaccination.
TNF-α inhibitors	Do not delay vaccination. No modification in TNF alpha treatment is needed.	TNF alpha inhibitors do not seem to have an impact on the effect of vaccination. Consider a safety margin of 14 days before and after administration of the vaccine in clinical stable patients.
Rituximab	Vaccination around 4 weeks before the next rituximab cycle.	Vaccination at least 4 weeks before or 6 months after rituximab is received.

**Both reviews remark that their recommendations are based on extrapolation from other vaccine studies and may change when data on COVID-vaccination in patients with rheumatic diseases become available.*

Conclusion

The COVID-19 pandemic has presented a challenge to clinicians caring for patients with sarcoidosis. Close monitoring of these patients is necessary as they may be at increased risk for worse COVID-19 outcomes compared to the general population, but is also complicated due to a decrease in hospital visits and pulmonary function test capacity. Home monitoring can be of great value to monitor patients and guide treatment decisions . As clinicians, we must be mindful of each patient's immunosuppressive regimen and continually assess the risk-benefit ratio of adjusting these medications. To provide further protection against disease, it is also advised to vaccinate sarcoidosis patients against COVID-19 International collaboration and large prospective patient registries could help to better understand COVID-19 outcomes in sarcoidosis in the near future.

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Chapter 6

Design of a randomized controlled trial to evaluate effectiveness of methotrexate versus prednisone as first-line treatment for pulmonary sarcoidosis: the PREDMETH study

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V. Kahlmann^{1*}, MD, M. Janssen Bonas^{2*}, MSc, C.C. Moor, MD¹,
C.H.M. van Moorsel, PhD², M. Kool, PhD¹, R. Kraaijevanger, MSc², J.C. Grutters,
MD PhD^{2,3}, M. Overgaauw⁴, M. Veltkamp, MD PhD^{2,3*}, M.S. Wijsenbeek,
MD PhD^{1*}, and Collaborating investigators

1. Centre of Excellence for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
2. ILD Center of Excellence, Department of Pulmonology, St. Antonius Hospital, Nieuwegein, the Netherlands
3. Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, The Netherlands
4. Sarcoidose.nl, sarcoidosis patient association, Alkmaar, the Netherlands

*These authors share first authorship

*These authors share last authorship

Abstract

Background

Treatment of pulmonary sarcoidosis is recommended in case of significant symptoms, impaired or deteriorating lung function. Evidence-based treatment recommendations are limited and largely based on expert opinion. Prednisone is currently the first-choice therapy and leads to short-term improvement of lung function. Unfortunately, prednisone often has side effects and may be associated with impaired quality of life. Methotrexate is presently considered second-line therapy and appears to have fewer side effects.

Objective

The primary objective of this trial is to investigate the effectiveness and tolerability of methotrexate as first-line therapy in patients with pulmonary sarcoidosis compared with prednisone. The primary endpoint of this study will be the change in hospital-measured forced vital capacity (FVC) between baseline and 24 weeks. Secondary objectives are to gain more insights into response to therapy in individual patients by home spirometry and patient-reported outcomes. Blood biomarkers will be examined to find predictors of response to therapy, disease progression and chronicity, and to improve our understanding of the underlying disease mechanisms.

Methods

In this prospective, randomized, non-blinded, multicenter, non-inferiority trial, we plan to randomize 138 treatment-naïve patients with pulmonary sarcoidosis who are about to start treatment. Patients will be randomized in a 1:1 ratio to receive either prednisone or methotrexate in a predefined schedule for 24 weeks, after which they will be followed up in regular care for up to 2 years. Regular hospital visits will include pulmonary function assessment, completion of patient-reported outcomes, and blood withdrawal. Additionally, patients will be asked to perform weekly home spirometry, and record symptoms and side effects via a home-monitoring application for 24 weeks.

Discussion

This study will be the first randomized controlled trial comparing first-line treatment of methotrexate with prednisone and will provide valuable data on efficacy, safety, quality of life and biomarkers. If this study confirms the hypothesis that methotrexate is as effective as prednisone as first-line treatment for sarcoidosis but with fewer side effects, this will lead to improvement in care and initiate a change in practice. Furthermore, insights into the immunological mechanisms underlying sarcoidosis pathology might reveal new therapeutic targets.

Trial registration

The study was registered on the 19th of March 2020 in the International Clinical Trial Registry, www.clinicaltrials.gov; ID NCT04314193.

Keywords

Sarcoidosis, prednisone, methotrexate, biomarkers, quality of life, home-monitoring

Background

Sarcoidosis is a multisystem, granulomatous disorder of unknown cause, which most commonly affects the lungs. Patients often have organ-specific symptoms such as dyspnea and cough, but many patients also suffer from a wide range of other disabling, non-specific symptoms including fatigue, stress, anxiety, depression, small-fiber neuropathy, decreased exercise tolerance, cognitive impairment, and chronic pain (1, 2). These symptoms have a major impact on quality of life (QoL) and social as well as work participation of sarcoidosis patients (1, 2). Treatment of pulmonary sarcoidosis should be considered for patients with significant pulmonary symptoms and patients with an impaired or deteriorating lung function (3, 4). The ATS/ERS/WASOG guideline, dating from 1999, recommends oral corticosteroids as the first-choice therapy for pulmonary sarcoidosis and this is also reflected in a recent Delphi consensus statement and current practice (5-7). These recommendations are mainly based on expert opinion and limited evidence from observational studies. Both state that more research is needed to define the best treatment for patients with pulmonary sarcoidosis (5-7). Although corticosteroid treatment leads to short-term improvement of pulmonary function, radiological improvement, and symptom reduction, previous studies have not conclusively demonstrated a beneficial effect in preventing disease progression in the long-term (3, 4, 7). Corticosteroids can have debilitating side effects, such as diabetes, osteoporosis, depression and weight gain (8-10). Long-term use of corticosteroids is associated with impaired QoL (11). Hence, there is a major need to find better treatment options for sarcoidosis with fewer side effects and less impact on QoL.

Methotrexate is most used as second-line therapy, when prednisone is ineffective or not tolerated, and appears to have fewer side effects (7, 12). Even though methotrexate is sometimes used as first-line therapy in case of (relative) contraindications for prednisone, no data on its effectiveness as first-line treatment for pulmonary sarcoidosis exist. A number of studies evaluated the efficacy of methotrexate as second-line treatment for sarcoidosis, and showed that methotrexate had a significant steroid-sparing effect and improved pulmonary function (13-16). Most commonly reported side effects in these studies were gastrointestinal complaints, headache, general malaise, and infections. These side effects only led to treatment discontinuation in a minority of cases. Moreover, according to a sarcoidosis expert survey, methotrexate seems to be safe and well tolerated when used for a prolonged period of time (12).

Tailoring of existing therapies and development of new treatments is also hampered by the incomplete understanding of the pathobiology of sarcoidosis (17). Biomarkers predictive of disease behaviour and response to therapy are highly needed to avoid overtreatment with unnecessary side effects in some patients and undertreatment with possible organ damage as a result in others. The ideal biomarker is highly sensitive, widely reproducible, rapidly available and low-priced. Unfortunately, none of the currently used biomarkers in sarcoidosis care fulfils these criteria (18). Available data indicate a role for specific T-cells, called Th17.1-cells, and cytokine expression in dendritic cells (DCs) in predicting disease course (19). Furthermore, higher numbers of intermediate and non-classical monocytes at baseline also seem related to response to therapy in patients treated with infliximab (20). Further advances in serum as well as cellular biomarker discovery can provide more insights into disease mechanisms, disease behaviour, and response to therapy. Home monitoring of lung function and patient-reported outcomes is a more clinical approach to assess response to treatment, as this will allow for more detailed information on treatment effect (8, 21). Together, this will contribute to personalized treatment of sarcoidosis.

This paper describes the design of the PREDMETH study, which will evaluate the efficacy of methotrexate as first-line treatment for pulmonary sarcoidosis compared with prednisone and aims to improve evidence-based treatment options and quality of life for patients with sarcoidosis.

Methods/design

Objectives and endpoints

The main objective of this study is to investigate the effectiveness and tolerability of methotrexate as first-line therapy in patients with pulmonary sarcoidosis compared with prednisone. The primary endpoint of this study is the change in hospital-measured Forced Vital Capacity (FVC) between baseline and 24 weeks. Secondary objectives are to gain more insights into response to therapy in individual patients by home spirometry and patient-reported outcomes. Furthermore, we aim to also examine blood biomarkers of disease progression and chronicity, to assess whether response to therapy can be predicted in individual patients, and to gain more insights into the underlying disease mechanism and potential new targets for therapy. **Table 1** shows the endpoints of the PREDMETH study.

Design and participants

The PREDMETH study is a prospective, randomized, non-blinded, multicenter, non-inferiority trial, designed to compare effectiveness and tolerability of methotrexate versus prednisone as first-line therapy for pulmonary sarcoidosis. The study is a joint design of clinicians, scientists and a patient expert panel. In this study, 18 centers in the Netherlands will participate. The study will randomize a total of 138 treatment-naïve adult sarcoidosis patients, about to start first-line therapy for a pulmonary indication.

Patients will be informed about the study by their treating physician. If patients are willing to participate, written informed consent will be obtained, and patients will be screened for eligibility. The in- and exclusion criteria are shown in **Table 2**. If eligible, patients will be randomized in a 1:1 ratio to receive either prednisone or methotrexate for 24 weeks, after which they will be followed up in regular care up to 2 years. For allocation of each subject to a treatment arm a centralized electronic randomization system will be used. Hospital visits will take place at 4, 16 and 24 weeks, and for long-term follow-up after 1 year and 2 years. Additionally, patients will be asked to perform weekly home spirometry and record symptoms and side effects via a home monitoring application for 24 weeks.

Table 1. Endpoints of the PREDMETH study listed as primary endpoint, secondary endpoints and explorative endpoints

Primary endpoint
Between-group difference in change in hospital-measured Forced Vital Capacity (FVC) % predicted between baseline and 24 weeks
Secondary endpoints
- Difference in change in FVC % predicted at 4, 16 weeks, 1 year and 2 years between prednisone and methotrexate group - Time to major pulmonary improvement measured by home-measured FVC, whereby major pulmonary improvement is defined as 80% of the maximum percent predicted FVC reached anywhere during the first 24 weeks of treatment - The percentage of patients with ≥5 and ≥10% improvement or decline in FVC at 4, 16 and 24 weeks - The percentage of patients with ≥10% improvement or decline in DLCO at 4, 16 and 24 weeks - Change over time in (Health-related) quality of life measured by King's Sarcoidosis Questionnaire (KSQ), Global Rating of Change scale (GRoC), Chronic Respiratory Questionnaire (CRQ) and Euroqol-5D-5L questionnaire (EQ5D-5L) at every clinical visit - Time to symptom improvement. Symptom scores are measured by Visual Analogue Scales (VAS), Medical Research Council dyspnea scale (MRC) and Fatigue Assessment Scale (FAS). - Expectations with medication at baseline - Experiences and satisfaction with medication measured by the Patient Experience and Satisfaction with Medication Questionnaire (PESaM) - Number, severity and impact of side effects compared between methotrexate and prednisone. - Number of patients who discontinue/switch medication - Adherence to treatment schedule (% of patients that received at least 90% of the total cumulative dose after 24 weeks) - Correlation between angiotensin converting enzyme (ACE), serum soluble interleukin-2 receptor (sIL-2R) and clinical parameters
Explorative endpoints
- Assess predictors of disease progression and response to therapy - Correlations between biomarker characteristics and clinical parameters - Change in biomarkers over time - Explore potential differences in distribution/phenotypes of monocytes, Th-cells, dendritic cells and new biomarkers identified using proteomics between patients during treatment with prednisone or methotrexate at all time points

Table 2: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Diagnosis of sarcoidosis according to the ATS/ERS/WASOG criteria (6), in case of absent histology, a diagnosis of sarcoidosis can also be established in a multidisciplinary team meeting in a sarcoidosis expert center based on a highly suggestive clinical and radiological picture (22) • Age ≥18 years • A pulmonary indication for treatment and parenchymal involvement on X-ray or chest CT-scan conducted within three months before inclusion (determined by the treating physician and according to current guidelines) • A forced vital capacity (FVC) of ≤90% of predicted, or a diffusion capacity of the lung for carbon monoxide (DLCO) ≤70% of predicted, or an absolute decline of ≥5% FVC, or an absolute ≥10% DLCO decline in the past year	• Any condition or circumstance that, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study procedures • Previous immunosuppressive treatment for sarcoidosis • Use of systemic immunosuppressive therapy within the preceding three months for another disease than sarcoidosis • Pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study treatment or within 90 days after the last dose in the randomized study phase. For males; planning to procreate during the study or within 90 days after the last dose of the randomized study phase • Primary systemic treatment indication being an extra pulmonary location of sarcoidosis (e.g. cardiac or neurological) • Contraindication for methotrexate or corticosteroids*

*Contra-indications for methotrexate or corticosteroids are defined as: severely impaired renal function (creatinine clearance <30 ml/min), impaired hepatic function (serum bilirubin-value >5 mg/dl or 85.5 micromole/l), bone marrow insufficiency with severe leukopenia, thrombocytopenia, or anaemia, severe acute or chronic infections, such as tuberculosis, human immunodeficiency virus, parasitic infections or other immunodeficiency syndromes, mouth, stomach or duodenal ulcers.

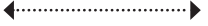
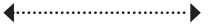
Hospital visits

Baseline characteristics of patients, such as gender, age, self-reported ethnicity, smoking status, comorbidity, co-medication, date of sarcoidosis diagnosis, details of organ involvement, and if available details of X-ray and chest CT scan will be recorded. At every visit, a physical examination will be performed to record weight, height, waist circumference and blood pressure of the patients. In-hospital pulmonary function measurements will include FVC, Forced Expiratory Volume in 1 second (FEV1) and diffusion capacity of the lung for carbon monoxide (DLCO). Furthermore, routine blood samples will be collected to assess blood count, kidney- and liver function. An additional sample of 80 ml blood will be taken for analysis of Angiotensin converting enzyme (ACE), serum soluble interleukin-2 receptor (sIL-2R), monocyte subsets, T-cells, dendritic cells, and proteomics biomarker discovery. Patients will also be asked to complete patient-reported outcome measures (PROMs) via a home monitoring app at every visit. The PROMs consist of the Fatigue Assessment Scale (FAS), the King’s Sarcoidosis Questionnaire (KSQ), Global Rating of Change Scale (GRoC), Chronic Respiratory Questionnaire (CRQ), Patient Experience and Satisfaction with Medication Questionnaire (PESaM), and Euroqol-5D-5L questionnaire (EQ5D-5L). At follow-up visits all adverse events will be evaluated and recorded. Side effects will be managed according to the discretion of the treating physician. Physicians can deviate from the treatment flowchart at any time, if the clinical situation demands so. A flow chart of the study design is shown in **Table 3**.

Treatment schedule

For prednisone the standard dosage according to literature is 20-40 mg daily (3, 7). Patients will start with 40 mg prednisone daily for 4 weeks. Subsequently, this dose will be tapered to a maintenance dose of 10 mg/day within 16 weeks. The maintenance dose will be continued until 24 weeks after start of treatment. After 24 weeks, prednisone is either continued at 10mg or further reduced at the discretion of the treating physician. According to current clinical recommendations patients will also receive calcium 500 mg/colecalciferol 400IU per day (6 days per week) and risedronic acid 35 mg once a week. In case of intolerable side effects of prednisone, the treating physician will start early tapering. If side effects remain intolerable, prednisone will be discontinued and patients will start on the methotrexate schedule.

Table 3: Study schedule of the PREDMETH trial

		STUDY PERIOD					
		Randomised phase				Follow-up phase	
TIMEPOINT		T1	T2	T3	T4	T5	T6
		baseline	4wks	16wks	24wks	1 year	2 years
ENROLMENT	Eligibility screen	X					
	Informed consent	X					
	Allocation	X					
INTERVENTIONS	Prednisone						
	Methotrexate						
ASSESSMENTS	Baseline characteristics	X					
	Physical examination	X	X	X	X	X	X
	Pulmonary function test	X	X	X	X	X	X
	Blood withdrawal	X	X	X	X	X	X
	Evaluation of adverse events		X	X	X	X	X
	Patient-reported outcomes	X	X	X	X	X	X
ONLINE HOME MONITORING	Home Spirometry	Three consecutive measurements once a week at the same day					
	Reporting of symptoms and side-effects	Weekly reporting of symptoms and side effects on the					

For methotrexate, the starting dosage will be 15 mg once a week, with folic acid 5 mg once a week. Subsequently, the dose will be increased to 25 mg/week within 8 weeks if tolerated. After 24 weeks, the dose of methotrexate is either continued or reduced at the discretion of the treating physician. Methotrexate will be discontinued if aspartate aminotransferase (AST) is >3 times the upper limit of normal. In case of intolerable side effects of methotrexate the total dose will be divided into twice weekly dosing. If side effect do not subside, oral methotrexate will be switched to subcutaneous methotrexate in the same dose. If side effects remain intolerable, dosage of subcutaneous methotrexate will be tapered according to the discretion of the treating physician. If side effects do not subside, methotrexate will be discontinued and the patient will start on the prednisone schedule. If an absolute FVC decline of ≥10% on in-hospital measurement of FVC is detected, the other treatment arm will be added to the current therapy (i.e. patients on methotrexate will additionally start with the prednisone schedule and patients on prednisone will additionally start with the methotrexate schedule). In this case, patients will be treated with both

methotrexate and prednisone and remain in the study. At any time, the treating physician may decide to deviate from this treatment schedule if the clinical situation demands so. **Figure 1** shows the treatment schedule of prednisone or methotrexate.

Home monitoring

For home monitoring of pulmonary function, symptoms and side effects, a home monitoring application will be used, which has previously been developed together with sarcoidosis patients (21). The application will be installed on a smartphone or tablet. In this CE-marked, secured application (Curavista, the Netherlands), patients will keep track of their own data, such as pulmonary function, side effects and symptoms. A graphic overview of results is available, so patients can gain more insight in their disease course, an example is shown in Figure 2. A handheld spirometer (Spirobank Smart, MIR, Italy) will be handed out to all patients. Patients will be instructed to undertake spirometry (three consecutive measurements) once a week at the same day, at approximately

the same time to enhance compliance and reduce variability (23). The best result of the day will be transmitted real-time to the patients' personal platform and will be directly accessible for both patients and the study team. This will enable close monitoring and early detection of possible deterioration. On the same day as spirometry, patients will report their symptoms and, if any, side effects on their personal platform. Patients record cough, dyspnea, fatigue, and general complaints on a visual analog scale (VAS) and will also report dyspnea on the Medical Research Council scale (MRC). In case of side effects, patients can record which side effects they have and how bothersome they are. When FVC declines $\geq 10\%$, or side effects are burdensome, an email alert will be sent directly to the treating physician, who will contact the patient within 24 hours to discuss symptoms and decide whether an extra outpatient clinic visit with pulmonary function measurement is needed. Furthermore, patients will be asked to complete PROMs at every time point before the doctor's visit.

Serum and cellular biomarkers

Blood samples will be analyzed in order to study both serum and cellular biomarkers. With regards to serum biomarkers, the value of existing biomarkers such as ACE and sIL-2R in predicting disease progression or response to therapy will be studied prospectively. Furthermore, a proteomics approach will be used to search for possible new biomarkers in sarcoidosis. Regarding cellular biomarkers, the amount of Th17-lineage cells, DCs and monocytes will be analyzed in order to predict response for individual patients to prednisone and/or methotrexate.

Sample size calculation

The power calculation is based on data from a previous observational study with prednisone in newly treated patients with pulmonary sarcoidosis. In this study, the mean increase in FVC with prednisone was 15%, with a standard deviation of 10.5% (8). In a case series of 50 patients with sarcoidosis treated with methotrexate, treatment effect was in line with the findings for prednisone; 66% of patients had more than 15% improvement in vital capacity after 6 months (24). We chose a non-inferiority margin of 5%, because FVC measurements show biological variation and thus variation $<5\%$ is not considered clinically relevant. Based on these numbers, using a one-sided test with a power of 80% (β) and a type 1 error of 5% (α), the estimated sample size of this study is 110 patients. To allow for 20% drop-out, we aim to randomize 138 patients.

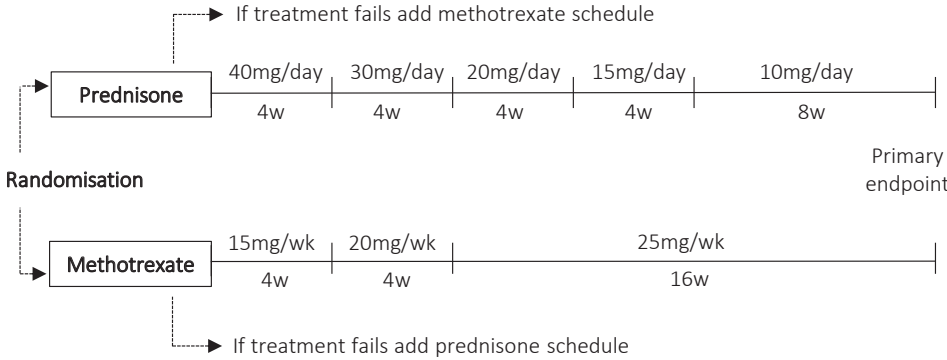


Figure 1. Flow chart of the treatment schedule for methotrexate and prednisone during the randomisation phase

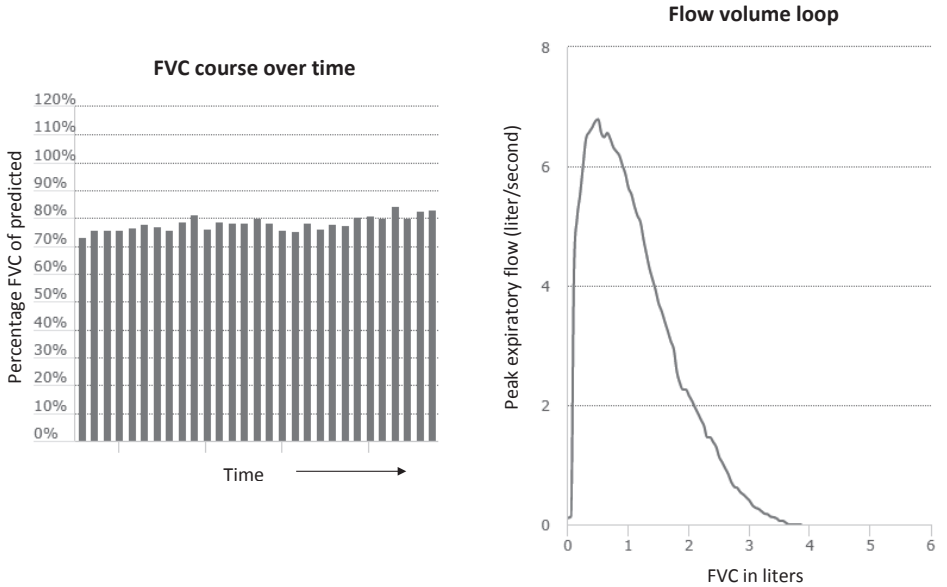


Figure 2. Example of home spirometry outcome, this graphical overview is available on patient's personale platform and is accessible for both patients and the study team

Statistical analyses

The primary analysis will be based on the Intention-to-Treat (ITT) population, defined as all randomized patients who received at least one dose of prednisone or methotrexate. Patients who discontinue treatment prematurely will be analyzed based on the available data. As a sensitivity analysis, a Per Protocol analysis will be performed in all enrolled patients who complete the 24 week treatment regimen

without major protocol violations. Change in FVC (% predicted) between baseline and 24 weeks follow-up will be compared between the two groups by using multilevel analysis with the repeated values of FVC as dependent variable and groups, time (defined as categorical variable) and baseline FVC as covariate. To account for the repeated FVC measurements, patient will be included as a random effect. Additionally the interaction terms between the time points and group will be added to assess at which point in time the groups have different average FVC values.

(Generalized) multilevel analyses will also be used to evaluate within and between-group differences in pulmonary function, symptoms, QoL scores, and side effects over the study period. Between-group differences in mean time to onset of side effects and time to symptom improvement will be analyzed using Kaplan-Meier and log rank test. The Chi-square test will be used to evaluate between-group differences in the proportions of patients who discontinue medication, proportion of patients who have FVC improvement and FVC decline, and the proportion of patients who adhere to the treatment schedule. The time to pulmonary improvement, using home spirometry, will be assessed using a linear mixed model, with FVC as dependent variable and time and treatment group as independent variables. Time will be entered as a random effect and will be modelled flexibly. Moreover, this model will incorporate the change in curvature of the FVC's temporal trajectory, and thus enable estimation of the time point at which the maximum improvement in lung function is reached. Correlation between lung function, side effects, QoL scores and symptoms will be analyzed with Pearson correlation coefficient. The FVC trajectory over time will be related to the trajectory of QoL scores over time with a linear mixed model. Logistic regression will be used to analyze which clinical or laboratory parameters are associated with disease progression (defined as $\geq 10\%$ FVC decline) and disease chronicity.

Discussion

There is a major unmet need for better evidence-based treatment in sarcoidosis. Although this has already been acknowledged in the ATS/ERS/WASOG guideline 20 years ago, research into first-line treatment options is still lacking. This will be the first study evaluating the efficacy of methotrexate as a first-line treatment for pulmonary sarcoidosis. As prednisone is often accompanied by many side effects, the possibility to choose for methotrexate as first-line therapy may potentially lead to a reduction in side effects and improvement in quality of life for patients. A non-inferiority design was chosen since we hypothesize that methotrexate is as effective as prednisone (non-inferiority margin considered), but has fewer side effects. We chose a non-blinded design because it would be practically impossible to integrate dosing and tapering schedules as described in a double-blind study.

Previous studies evaluated the efficacy of methotrexate as second-line therapy and showed a steroid-sparing effect and significant increase in pulmonary function. In these trials, dosages between 10-15 mg methotrexate were used (14, 15). In the current trial, methotrexate will be initiated at 15 mg and, if tolerated, subsequently increased until 25mg. This treatment schedule is chosen based on experiences with methotrexate in rheumatoid arthritis, for which starting dosages of 15mg/week escalating with 5mg/month to 25-30mg/week have been demonstrated to have the best clinical efficacy (25). By using an online home monitoring program, potential side effects will be closely monitored and where needed, medication will be adjusted. The study design and treatment schedule have been developed together with a patient panel, to ensure that the burden of study participation will be acceptable for patients.

Next to side effects and symptoms, the home monitoring program also allows for close monitoring of lung function. A previous observational study in patients with pulmonary sarcoidosis, newly treated with prednisone, showed that home spirometry can reliably detect changes in pulmonary function in sarcoidosis patients and assess the time to pulmonary improvement (8). The major increase in FVC already occurred within the first month of treatment; however, until now no consensus exists on the optimal tapering schedule (7). The PREDMETH trial will also provide data on time to pulmonary improvement in patients treated with methotrexate, which are currently lacking. The online home monitoring program that will be used in the current study, has been previously evaluated together with sarcoidosis patients in a pilot study. This study showed that patient

satisfaction and compliance were high, and the reproducibility of FVC was good (21). Thus, home monitoring will allow us to better evaluate (early) response to therapy, could enable personalized tapering of medication in the future, and will provide more insights in the balance of effects and side effects in newly-treated sarcoidosis patients.

Next to the important clinical aims of the study, the role of serum and cellular biomarkers in disease pathogenesis as well as predicting disease outcome will be further explored (26). By combining these insights with the clinical outcomes of the study this trial will hopefully provide unique insights into the development and disease course of pulmonary sarcoidosis.

In conclusion, by conducting a randomized clinical trial to compare prednisone and methotrexate as first line treatment of pulmonary sarcoidosis we expect to advance evidence based treatment practice for sarcoidosis. Furthermore, seamlessly integrating translational research on patient samples from this trial will provide more insights not only with regard to tailored treatment, but also in the pathophysiological mechanisms of sarcoidosis. All together, we believe that the proposed study has the potential to enhance evidence-based and personalized therapy that improves outcomes and quality of life for patients with sarcoidosis.

Collaborating investigators

B. Koopman, MD. PhD, Department of Pulmonary Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands. J.J.M. Geelhoed, MD. PhD, Department of Pulmonary Medicine, Leiden University Medical Center, Leiden, the Netherlands. R. Janssen, MD. PhD, Department of Pulmonary Medicine, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands. R.E. Jonkers, MD. PhD, Department of Pulmonary Medicine, Amsterdam UMC, Academisch Medisch Centrum, Amsterdam, The Netherlands. H. Kramer, MD, PhD, Department of Pulmonary Medicine, Martini Hospital, Groningen, the Netherlands. L. Moonen, MD, Department of Pulmonary Medicine, Rijnstate Hospital, Arnhem, the Netherlands. R.L.M. Mostard, MD. PhD, Department of Pulmonary Medicine, Zuyderland Medical Center, Heerlen, the Netherlands. E.J Nossent, MD. PhD, Department of Pulmonary Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. M.J. Overbeek, MD. PhD, Department of Pulmonary Medicine, Haaglanden Medical Center, Den Hague, the Netherlands. R.H.N.A.J. van Rijswijk, MD, Department of Pulmonary Medicine, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands. M. Wagenaar, MD. PhD, Department of Pulmonary Medicine,

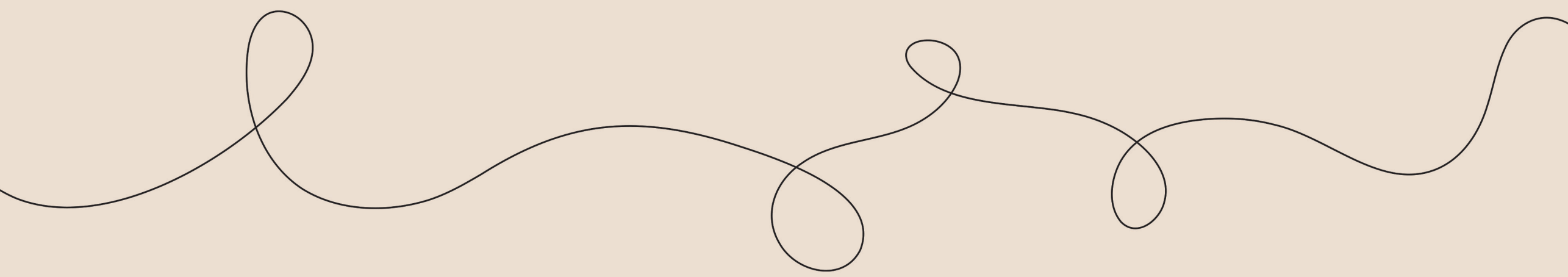
Medisch Spectrum Twente, Enschede, the Netherlands. S. Walen, MD, Department of Pulmonary Medicine, Isala Klinieken, Zwolle, the Netherlands. P.L.M.L. Wielders, MD, Department of Pulmonary Medicine, Catharina Hospital, Eindhoven, the Netherlands. D.W. Loth, MD. PhD, Department of Pulmonary Diseases, Amphia hospital, Breda, The Netherlands. B.A.H.A. Bogaarts, MD. PhD, Department of Pulmonary Diseases, VieCuri Medical Center, The Netherlands. J. van der Maten, MD. Department of Pulmonary Diseases, Medical Center Leeuwarden, The Netherlands.

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Chapter 7

First-Line Treatment of Pulmonary Sarcoidosis with Prednisone or Methotrexate



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Vivienne Kahlmann¹, Montse Janssen Bonás², Catharina C. Moor¹,
Jan C. Grutters^{2,3}, Rémy L.M. Mostard^{4,5}, Henricus N.A.J. van Rijswijk⁶,
Jan van der Maten⁷, Emiel R. Marges⁸, Linda A.A. Moonen⁹, Maria J. Overbeek^{8,10},
Bart Koopman¹¹, Daan W. Loth¹², Esther J. Nossent¹³, Michiel Wagenaar¹⁴,
Henk Kramer¹⁵, Pascal L.M.L. Wielders¹⁶, Peter I. Bonta¹⁷, Stefan Walen¹⁸,
Brigitte A.H.A. Bogaarts¹⁹, René Kerstens²⁰, Mayka Overgaauw²¹, Marcel
Veltkamp^{2,3}, and Marlies S. Wijsenbeek¹, and PREDMETH collaborators

* Affiliations of the authors are provided in the supplement

Abstract

Background

Prednisone is currently recommended as the first-line treatment for pulmonary sarcoidosis but is associated with many side effects. Methotrexate, which is recommended as a second-line treatment, appears to have fewer side effects than prednisone but a slower onset of action. Data are needed on the efficacy and side-effect profile of methotrexate as compared with prednisone as first-line treatment for pulmonary sarcoidosis.

Methods

In this multicenter, open-label, noninferiority trial involving patients with pulmonary sarcoidosis who had not previously received treatment, we randomly assigned patients, in a 1:1 ratio, to receive prednisone or methotrexate according to a prespecified treatment schedule. The primary end point was the mean change from baseline to week 24 in the percentage of the predicted forced vital capacity (FVC), as estimated with the use of mixed models for repeated measures. The noninferiority margin for the primary end point was 5 percentage points.

Results

Of the 138 patients who underwent randomization, 70 were assigned to receive prednisone and 68 to receive methotrexate. The unadjusted mean change from baseline to week 24 in the percentage of the predicted FVC was 6.75 percentage points (95% confidence interval [CI], 4.50 to 8.99) in the prednisone group and 6.11 percentage points (95% CI, 3.72 to 8.50) in the methotrexate group. Methotrexate was noninferior to prednisone with regard to the primary end point, with an adjusted between-group difference of -1.17 percentage points (95% CI, -4.27 to 1.93). Adverse events occurred in a similar percentage of patients in the two trial groups. Weight gain, insomnia, and increased appetite were the most common adverse events with prednisone, and nausea, fatigue, and any abnormal liver-function test were among the most common adverse events with methotrexate.

Conclusions

In patients with pulmonary sarcoidosis, initial treatment with methotrexate was noninferior to that with prednisone with regard to the change from baseline to week 24 in the percentage of the predicted FVC. Differences in the side-effect profile between methotrexate and prednisone may inform shared decision making by providers and patients about the appropriate treatment approach. (Funded by the Dutch Lung Foundation; PREDMETH ClinicalTrials.gov number, [NCT04314193](https://clinicaltrials.gov/ct2/show/study/NCT04314193).)

Introduction

Sarcoidosis is a systemic inflammatory disease characterized by the development of granulomas, which can occur in almost any organ. The lungs are most often affected, and involvement of the lungs is the leading cause of worsened health and death among persons with sarcoidosis (1-3). Treatment is aimed at decreasing morbidity and mortality and improving quality of life (2-4).

International guidelines recommend prednisone as the first-line treatment for pulmonary sarcoidosis (4,5). However, this recommendation is based on low-quality evidence in the absence of well-designed trials (4). Prednisone may lead to short-term improvement of pulmonary function, decreased symptoms, and decreased radiologic abnormalities (6-8). However, prednisone often causes side effects such as weight gain, sleep problems, hypertension, and diabetes, which may reduce quality of life and could lead to long-term adverse effects on health (9,10). In patients with pulmonary sarcoidosis, an urgent need exists for better evidence-based treatment strategies with fewer toxic effects.

Methotrexate is recommended as a second-line treatment for sarcoidosis and may have fewer side effects than prednisone (11). The most frequent side effects of methotrexate treatment include gastrointestinal events, general malaise, and infections (11-13). Methotrexate is thought to have a slower onset of action than prednisone, but studies substantiating this view are lacking. Observational and interventional studies have suggested that the use of methotrexate as second-line treatment can lead to substantial tapering of glucocorticoids and improvement in pulmonary function (13-16). In an observational study in which methotrexate was administered to patients with a contraindication to glucocorticoid therapy, the efficacy and safety profile of methotrexate appeared to be similar to that of prednisone; however, the results should be interpreted with caution owing to the observational design of the study and the lack of well-defined end points (17).

Prospective randomized trials investigating first-line treatments in patients with pulmonary sarcoidosis are lacking. Therefore, we conducted the PREDMETH trial to investigate the efficacy and side-effect profile of methotrexate as compared with prednisone as first-line treatment for pulmonary sarcoidosis.

Methods

Trial Design and Oversight

The PREDMETH trial was an open-label, randomized, noninferiority trial conducted at 17 hospitals in the Netherlands. The trial was designed by clinicians, researchers, and patients from the Dutch Sarcoidosis Patient Association and was conducted in accordance with the trial protocol (available with the full text of this article at NEJM.org) and with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice of the International Council for Harmonisation (18). Approval was obtained from the medical ethics committee at the Erasmus Medical Center and the local ethics committee at each trial site. Written informed consent was obtained from all the patients. All the authors gathered the data. An independent statistician who was unaware of the treatment assignments before the database lock performed the primary analyses. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Adult patients with pulmonary sarcoidosis (as defined by the American Thoracic Society, European Respiratory Society (ERS), and World Association for Sarcoidosis and Other Granulomatous Disorders (19)) who had not previously received treatment were eligible for inclusion. The inclusion criteria were a pulmonary indication to initiate treatment (defined as moderate or severe symptoms and pulmonary sarcoidosis associated with a risk of worsened health or death), in line with the current ERS guideline recommendations (4); a forced vital capacity (FVC) of less than 90% of the predicted value, a diffusing capacity of the lungs for carbon monoxide (DLco) of less than 70% of the predicted value, a decrease of at least 5 percentage points in the predicted FVC, or a decrease of at least 10 percentage points in the predicted DLco in the previous 12 months; and parenchymal abnormalities as determined by investigators at the local trial sites. Exclusion criteria are provided in **Table S1** in the Supplementary Appendix (available at NEJM.org).

Patients were randomly assigned in a 1:1 ratio to receive prednisone or methotrexate for 24 weeks according to a prespecified treatment schedule (**Figure S1**). Randomization was performed with the use of a centralized electronic system. Oral prednisone treatment was initiated at a dose of 40 mg per day and was tapered every 4 weeks until a maintenance dose of 10 mg per day was established at week 16. Oral methotrexate treatment was initiated at a dose of 15 mg per week and

was increased by 5 mg per week every 4 weeks to a maximum dose of 25 mg per week if the side-effect profile was acceptable. If side effects occurred, adjustments to the dose of prednisone or methotrexate or to the route of methotrexate administration could be made according to a prespecified plan. If unacceptable side effects persisted, patients could switch to the other treatment group. In case of insufficient efficacy, which was defined as a decrease from baseline of at least 10 percentage points in the percentage of the predicted FVC, the other treatment was added to the current treatment. All the patients were asked to attend every trial visit, regardless of whether they had discontinued the trial treatment.

End Points and Assessments

The primary end point was the mean change from baseline to week 24 in the percentage of the predicted FVC. The secondary end points were the change in the FVC, measured in liters, at week 24; an increase of at least 5 percentage points in the percentage of the predicted FVC at week 24; a decrease of at least 5 percentage points in the percentage of the predicted FVC at week 24; the change in the percentage of the predicted DLco at week 24; an increase of at least 10 percentage points in the percentage of the predicted DLco at week 24; a decrease of at least 10 percentage points in the percentage of the predicted DLco at week 24; and the changes in the King's Sarcoidosis Questionnaire (KSQ) health status domain and lung domain scores (20-22), the Fatigue Assessment Scale (FAS) score (23,24), and the EuroQol Group 5-Dimension 5-Level (EQ-5D-5L) questionnaire descriptive health index score and visual analogue scale (VAS) score (25), all at week 24.

The KSQ general health status domain score ranges from 0 to 100, with higher scores indicating better health status; the KSQ lung domain score ranges from 0 to 100, with higher scores indicating fewer symptoms (20). The minimal clinically important difference is 8 points for the general health status domain and 4 points for the lung domain (21). The FAS is used to assess fatigue; scores range from 10 to 50, with higher scores indicating worse fatigue. The minimal clinically important difference is 4 points (23,24). The EQ-5D-5L is used to assess health outcomes. Scores on the descriptive health index range from 0 (death) to 1 (full health); scores on the VAS range from 0 to 100, with higher scores indicating better health status. The minimal clinically important differences for the descriptive health index and the VAS are unknown in patients with sarcoidosis and 0.065 and 6.9 points, respectively, in patients with chronic obstructive pulmonary disease (26).

We administered the Patient Experiences and Satisfaction with Medications (PESaM) questionnaire at week 24. The PESaM is used to assess medications with regard to experiences, satisfaction, and importance as reported by the patient. A Likert scale is used to assess experiences and importance (scores range from 0 to 4, with higher scores indicating more positive experiences and greater importance), and a Likert-type scale is used to assess satisfaction (scores range from -5 to 5, with lower scores indicating greater dissatisfaction and higher scores greater satisfaction). The minimal clinically important difference for each score on the PESaM is not known in patients with sarcoidosis (**Table S2**) (27).

Levels of soluble interleukin-2 receptor in serum were measured with the use of enzyme immunoassays, in accordance with the instructions of the manufacturer (IBL International, part of the Tecan Group). Safety was assessed by the recording of adverse events and the monitoring of clinical status. Adverse events were coded according to the Medical Dictionary for Regulatory Activities, version 27.1.

Pulmonary function, patient-reported outcomes, and adverse events were assessed at baseline and at weeks 4, 16, and 24. The first database lock was performed after the last patient completed the week 24 visit.

Statistical Analysis

The trial was designed to assess the noninferiority of methotrexate as compared with prednisone regarding the difference in the mean change from baseline to week 24 in the percentage of the predicted FVC (primary end point). We determined that a sample size of 110 patients would provide the trial with 80% power to assess noninferiority at a two-sided significance level of 0.05, with a noninferiority margin of 5 percentage points. The sample-size calculation assumed a standard deviation of 10.5 percentage points for the primary end point (28) in both groups and no difference between the groups in the percentage of the predicted FVC at week 24. Accounting for an estimated loss to follow-up or withdrawal of 20%, we aimed to include 138 patients.

The primary analysis was conducted in the modified intention-to-treat population, defined as all the patients who underwent randomization and received at least one dose of prednisone or methotrexate. In the primary analysis, the difference between methotrexate and prednisone regarding the mean change in the percentage of the predicted FVC (with its 95% confidence interval) at week 24 was estimated with the use of mixed models for repeated measures that included the percentage of the predicted FVC at each visit as dependent

variables; treatment, visit, and treatment-by-visit interaction as factors; and the percentage of the predicted FVC at baseline as a covariate. Noninferiority was confirmed if the lower limit of the 95% confidence interval for the between-group difference in the mean change at week 24 was greater than -5 percentage points (noninferiority margin).

Mixed models for repeated measures that were similar to those used in the primary analysis were used to assess between-group changes in the percentage of the predicted FVC at week 24 in the per-protocol population, which included all the patients who received prednisone or methotrexate according to the prespecified treatment schedule at least 80% of the time. Similar mixed models for repeated measures were also used to calculate changes in the FVC (measured in liters), the percentage of the predicted DLco, the KSQ general health status and lung domain scores, the FAS score, the EQ-5D-5L scores, and the soluble interleukin-2 receptor level.

The Cochran–Mantel–Haenszel test was used to evaluate between-group differences in the percentage of patients with an increase or decrease of at least 5 percentage points in the percentage of the predicted FVC or an increase or decrease of at least 10 percentage points in the percentage of the predicted DLco at week 24. PESaM data were tabulated according to treatment group. Adverse events that started before the week 24 visit and adverse events that were ongoing at the week 24 visit were tabulated according to treatment group. A post hoc analysis of the change at week 24 in the percentage of the predicted forced expiratory volume in 1 second (FEV1) was conducted.

Secondary end points were not controlled for multiplicity. Results are reported as point estimates and 95% confidence intervals, and the widths of these confidence intervals should not be used to infer definitive treatment effects.

Results

Patients

From July 17, 2020, through February 22, 2024, we enrolled 138 patients; 70 were randomly as-signed to receive prednisone and 68 to receive methotrexate (**Figure S2**). One patient in the prednisone group was excluded because of an alternative diagnosis (silicosis). Baseline characteristics appeared to be generally balanced between the two groups (**Table 1**). The patients were generally representative of the population with pulmonary sarcoidosis, although the trial included a higher percentage of men (**Table S3**).

Table 1. Baseline Characteristics of the Patients (Modified Intention-to-Treat Population).*

Characteristic	Prednisone (N = 69)	Methotrexate (N = 68)	Total (N = 137)
Male sex — no. (%)	54 (78)	47 (69)	101 (74)
Age — yr	48.5±10.6	44.7±12.8	46.6±11.9
Smoking history — no. (%)			
Never smoked	46 (67)	37 (54)	83 (61)
Current smoker	4 (6)	7 (10)	11 (8)
Former smoker	19 (28)	24 (35)	43 (31)
Race — no. (%)†			
White	58 (84)	59 (87)	117 (85)
Black	5 (7)	5 (7)	10 (7)
Other	6 (9)	4 (6)	10 (7)
Scadding stage — no./total no. (%)‡			
Stage 2	35/44 (80)	34/48 (71)	69/92 (75)
Stage 3	1/44 (2)	9/48 (19)	10/92 (11)
Stage 4	8/44 (18)	5/48 (10)	13/92 (14)
Pattern on chest CT — no./total no. (%)			
Parenchymal abnormalities with lymphadenopathy	53/63 (84)	49/63 (78)	102/126 (81)
Parenchymal abnormalities without lymphadenopathy	1/63 (2)	8/63 (13)	9/126 (7)
Pulmonary fibrosis	9/63 (14)	6/63 (10)	15/126 (12)
Time since diagnosis — yr	2.0±3.5	1.5±4.4	1.7±4.0
Disease duration — no. (%)			

Table 1. Continued

Characteristic	Prednisone (N = 69)	Methotrexate (N = 68)	Total (N = 137)
<2 yr	51 (74)	58 (85)	109 (80)
2–5 yr	10 (14)	7 (10)	17 (12)
>5 yr	8 (12)	3 (4)	11 (8)
Body composition§			
Weight — kg	81.7± 15.9	84.9±18.8	83.3±17.4
Waist circumference — cm	95.1±12.1	96.6±15.8	95.8±14.0
Body-mass index	26.1±4.5	26.6±5.9	26.4±5.2
FVC			
Mean — liters	3.7±0.9	3.7±1.1	3.7±1.0
Percentage of predicted value	79.8±15.4	74.8±12.7	77.3±14.3
FEV ₁			
Mean — liters	2.64±0.64	2.67±0.78	2.66±0.71
Percentage of predicted value	71.4±16.2	68.3±13.4	69.9±14.9
Ratio of FEV ₁ to FVC	0.71±0.09	0.73±0.11	0.72±0.10
DLco¶			
Mean — mmol/min/kPa	6.7±1.6	6.9±2.1	6.8±1.9
Percentage of predicted value	69.8±13.8	69.3±15.7	69.6±14.8
King's Sarcoidosis Questionnaire scores			
General health status domain	63.3±13.2	59.4±13.5	61.3±13.5
Lung domain	60.5±14.5	59.4±15.1	59.9±14.7
Fatigue Assessment Scale score**	25.1±8.1	25.9±8.2	25.5±8.2
EQ-5D-5L questionnaire scores††			
Descriptive health index	0.8±0.2	0.7±0.2	0.8±0.2
Visual analogue scale	65.1±21.8	60.6±20.2	62.8±21.0
Soluble interleukin-2 receptor level — U/ml‡‡	164.4±106.2	176.8±94.4	170.6±100.3

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. Patient-reported outcomes were assessed no more than 7 days after baseline. CT denotes computed tomography, FEV₁ forced expiratory volume in 1 second, and FVC forced vital capacity.

† Race was reported by the patient.

Table 1. Continued

- ‡ The Scadding criteria for staging pulmonary sarcoidosis are defined by findings on chest radiography, with stage 0 indicating normal findings, stage 1 hilar lymphadenopathy, stage 2 bilateral hilar lymphadenopathy and pulmonary infiltrates, stage 3 pulmonary infiltrates without bilateral hilar lymphadenopathy, and stage 4 pulmonary fibrosis. Data were from chest radiographs obtained within the previous 3 months and were available in 92 patients.
- § Data on weight and body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for 1 patient in the methotrexate group. Data on waist circumference were missing for 4 patients in the methotrexate group.
- ¶ Values of the diffusing capacity of the lungs for carbon monoxide (DLco) were corrected for hemoglobin level.
- || Scores on the King's Sarcoidosis Questionnaire general health status domain (range, 0 to 100; higher scores indicate better health status) and lung domain (range, 0 to 100; higher scores indicate fewer symptoms) were missing for 10 patients in the prednisone group and for 7 patients in the methotrexate group.
- ** Scores on the Fatigue Assessment Scale (range, 10 to 50; higher scores indicate worse fatigue) were missing for 10 patients in the prednisone group and for 7 patients in the methotrexate group.
- †† Scores on the EuroQol Group 5-Dimension 5-Level (EQ-5D-5L) questionnaire descriptive health index (range, 0 [death] to 1 [full health]) and visual analogue scale (range, 0 to 100; higher scores indicate better health status) were missing for 10 patients in the prednisone group and for 8 patients in the methotrexate group.
- ‡‡ Normal values are less than 44 U per milliliter. Data were missing for 5 patients in the prednisone group and for 4 patients in the methotrexate group.

Efficacy

The mean ($\pm$ SD) daily dose of the assigned medication up to week 24 was 21.1 ± 2.1 mg in the prednisone group and 20.1 ± 3.0 mg in the methotrexate group (Table S5.1). The primary end-point analysis was conducted in the modified intention-to-treat population, which included 135 patients. The unadjusted mean change from baseline in the percentage of the predicted FVC at week 24 was 6.75 percentage points (95% confidence interval [CI], 4.50 to 8.99) in the prednisone group and 6.11 percentage points (95% CI, 3.72 to 8.50) in the methotrexate group (Figure 1A and Table S4.1). The between-group difference in the least-squares mean change at week 24 was -1.17 percentage points (95% CI, -4.27 to 1.93), which indicated that methotrexate was noninferior to prednisone (Figure 1B). The per-protocol analysis, which included 112 patients, also showed that methotrexate was noninferior to prednisone at week 24, with a between-group difference in the least-squares mean change of -1.40 percentage points (95% CI, -4.85 to 2.05) (Table S4.2).

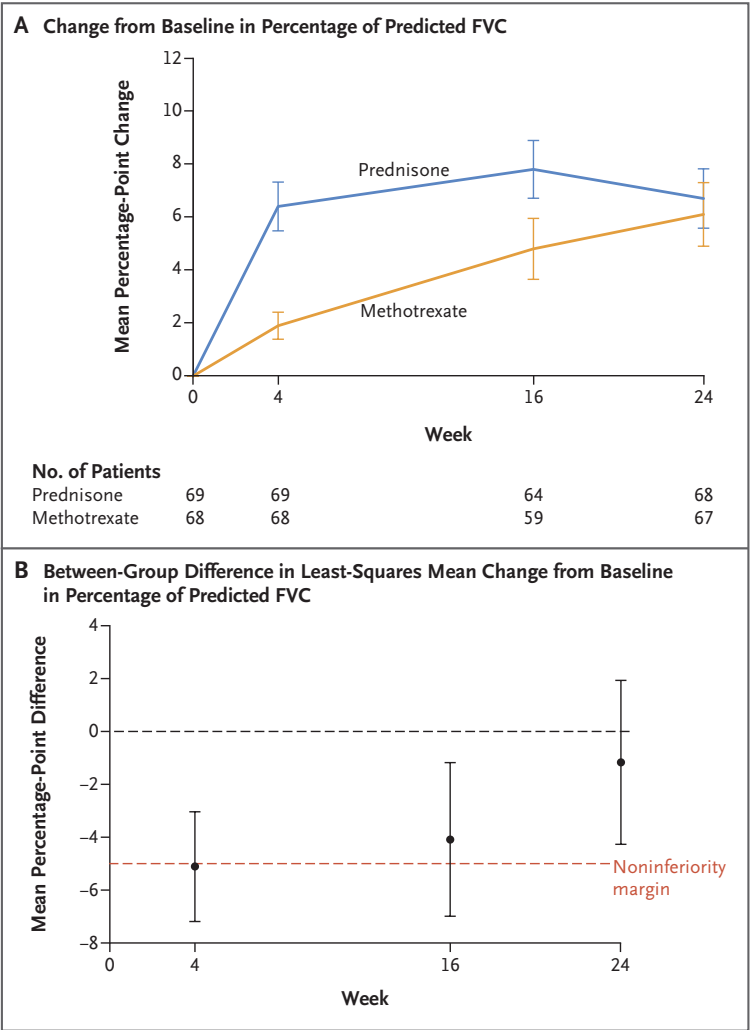


Figure 1. Change in Percentage of Predicted Forced Vital Capacity (Modified Intention-to-Treat Analysis). Panel A shows the unadjusted mean change in the percentage of the predicted forced vital capacity (FVC) in the prednisone and methotrexate groups between baseline and weeks 4, 16, and 24. The unadjusted mean change at week 24 (primary end point) was 6.75 percentage points (95% CI, 4.50 to 8.99) in the prednisone group and 6.11 percentage points (95% CI, 3.72 to 8.50) in the methotrexate group. Panel B shows the between-group difference in the least-squares mean change in the percentage of the predicted FVC between baseline and weeks 4, 16, and 24. The between-group difference at week 24 was -1.17 percentage points (95% CI, -4.27 to 1.93), which indicated that methotrexate was noninferior to prednisone. Point estimates and 95% confidence intervals were calculated with the use of mixed models for repeated measures that included treatment, visit, and treatment-by-visit interaction as factors and the percentage of the predicted FVC at baseline as the covariate. I bars indicate 95% confidence intervals.

Table 2. Secondary End Points at Week 24.*

End Point	Prednisone (N = 69)	Methotrexate (N = 68)	Difference (95% CI)†
Pulmonary function			
Change in FVC — liters‡	0.34±0.05	0.25±0.07	-0.08 (-0.25 to 0.09)
Increase of ≥5 percentage points in percentage of predicted FVC — no./total no. (%)	37/68 (54)	34/67 (51)	—
Decrease of ≥5 percentage points in percentage of predicted FVC — no./total no. (%)	6/68 (9)	2/67 (3)	—
Change in percentage of predicted DLco§	4.26±1.11	3.72±1.22	-0.43 (-3.43 to 2.57)
Increase of ≥10 percentage points in percentage of predicted DLco — no./total no. (%)	17/65 (26)	15/66 (23)	—
Decrease of ≥10 percentage points in percentage of predicted DLco — no./total no. (%)	3/65 (5)	3/66 (5)	—
Patient-reported outcomes			
Change in King's Sarcoidosis Questionnaire score¶			
General health status domain	4.80±1.63	8.18±1.67	2.50 (-1.88 to 6.88)
Lung domain	7.32±1.64	9.77±2.29	2.88 (-2.20 to 7.97)
Change in Fatigue Assessment Scale score	-2.62±0.75	-1.57±0.99	1.41 (-0.79 to 3.61)
Change in EQ-5D-5L questionnaire score			
Descriptive health index	0.06±0.02	0.04±0.02	0.01 (-0.05 to 0.06)
Visual analogue scale	2.70±3.03	7.16±3.06	-1.49 (-8.66 to 5.68)
Biomarkers			
Soluble interleukin-2 receptor level — U/ml**	-82.7±12.80	-81.1±12.98	10.90 (-8.91 to 30.72)

* Plus-minus values are means ±standard error. Shown are changes at week 24 as compared with baseline.

† Differences (methotrexate group minus prednisone group) and 95% confidence intervals were calculated with the use of mixed models for repeated measures that included treatment, visit, and treatment-by-visit interaction as factors and the percentage of the predicted FVC at baseline as a covariate. Secondary end points were not controlled for multiplicity; therefore, the confidence intervals should not be used to infer definitive treatment effects.

‡ Data were missing for 1 patient in the prednisone group and for 1 patient in the methotrexate group.

§ Data were missing for 4 patients in the prednisone group and for 2 patients in the methotrexate group.

¶ Data were missing for 22 patients in the prednisone group and for 21 patients in the methotrexate group.

|| Data were missing for 23 patients in the prednisone group and for 21 patients in the methotrexate group.

** Normal values are less than 44 U per milliliter. Data were missing for 12 patients in the prednisone group and for 10 patients in the methotrexate group.

Table 3. Adverse Events in the Overall Population.*

Event	Prednisone (N = 69)		Methotrexate (N = 68)	
	All Adverse Events	Ongoing Adverse Events at Wk 24	All Adverse Events	Ongoing Adverse Events at Wk 24
≥1 Adverse event — no. of patients (%)	65 (96)	—	65 (94)	—
Total no. of adverse events	308	165	283	104
Serious adverse events — no. of patients (%)†	3 (4)	NA	7 (10)	NA
Adverse events that led to treatment discontinuation or switch in treatment group — no. of patients (%)	10 (14)	NA	9 (13)	NA
Most common adverse events — no. of patients (%)‡				
Endocrine disorders				
Cushingoid appearance	10 (14)	6 (9)	2 (3)	2 (3)
Gastrointestinal disorders				
Abdominal pain	2 (3)	1 (1)	11 (16)	2 (3)
Diarrhea	4 (6)	1 (1)	10 (15)	2 (3)
Reflux	8 (12)	2 (3)	4 (6)	1 (1)
Nausea	6 (9)	0	25 (37)	9 (13)
General disorders				
Fatigue	7 (10)	5 (7)	18 (26)	10 (15)
Increased appetite	13 (19)	9 (13)	3 (4)	2 (3)
Malaise	3 (4)	1 (1)	10 (15)	1 (1)
Infections				
Respiratory tract infection	1 (1)	0	10 (15)	1 (1)
Investigations				
Abnormal liver-function tests				
Any test	2 (3)	2 (3)	17 (25)	8 (12)
Aspartate aminotransferase test: >3× ULN	1 (1)	0	2 (3)	1 (1)
Alanine aminotransferase test: >3× ULN	0	0	6 (9)	1 (1)
Weight gain	30 (43)	27 (39)	5 (7)	5 (7)
Musculoskeletal and connective-tissue disorders				
Myalgia	10 (14)	5 (7)	7 (10)	3 (4)
Nervous system disorders				
Headache	8 (12)	3 (4)	10 (15)	2 (3)
Psychiatric disorders				
Insomnia	29 (42)	11 (16)	4 (6)	2 (3)

Table 3. Adverse Events in the Overall Population.*

Event	Prednisone (N = 69)		Methotrexate (N = 68)	
	All Adverse Events	Ongoing Adverse Events at Wk 24	All Adverse Events	Ongoing Adverse Events at Wk 24
Mood swings	9 (13)	5 (7)	5 (7)	4 (6)
Nervousness	8 (12)	2 (3)	1 (1)	1 (1)
Respiratory disorders				
Productive cough	9 (13)	5 (7)	8 (12)	4 (6)
Skin and subcutaneous tissue disorders				
Rash	7 (10)	3 (4)	13 (19)	4 (6)

* NA denotes not applicable, and ULN upper limit of the normal range.

† The following serious adverse events were reported in the prednisone group: diabetes mellitus (assessed by the investigator as being related to treatment), pulmonary embolism (unrelated to treatment), and elective ureteral stent insertion (unrelated to treatment). The following serious adverse events were reported in the methotrexate group: arrhythmia supraventricular, dyspnea, multiple traumatic fractures, and afferent loop syndrome (all unrelated to treatment) and coronavirus disease 2019, respiratory tract infection, and gastroenteritis (all possibly related to treatment).

‡ Shown are adverse events reported in more than 10% of patients in either treatment group. Events were coded according to preferred terms in the *Medical Dictionary for Regulatory Activities*, version 27.1.

Secondary End Points

Secondary end points related to pulmonary function are shown in **Table 2**. An increase of at least 5 percentage points in the percentage of the predicted FVC between baseline and week 24 occurred in 37 patients (54%) in the prednisone group and in 34 patients (51%) in the methotrexate group.

In a post hoc analysis, the change in the percentage of the predicted FEV1 at week 24 was 6.24 percentage points (95% CI, 3.94 to 8.55) in the prednisone group and 5.73 percentage points (95% CI, 3.55 to 7.92) in the methotrexate group. Changes through week 24 in the KSQ lung domain score and general health status domain score, EQ-5D-5L VAS score, FAS score, and soluble interleukin-2 receptor level are shown in **Figure 2** and **Tables S6.1** through **S6.5**. PESaM scores at week 24 were generally similar in the prednisone and methotrexate groups (**Table S7**).

Safety

A summary of the most common adverse events is provided in **Table 3**. A total of 308 adverse events occurred in the prednisone group, and 283 adverse events occurred in the methotrexate group. At least one adverse event occurred in 96% of the patients in the prednisone group and in 94% of those in the methotrexate group. Serious adverse events occurred in 3 patients (4%) and 7 patients (10%), respectively. A total of 165 adverse events (54%) in the prednisone group and 104 (37%) of those in the methotrexate group were ongoing at week 24. Adverse events that led to the discontinuation of treatment or a switch to the other treatment group occurred in 10 patients (14%) in the prednisone group and in 9 patients (13%) in the methotrexate group (**Table 3** and **Table S8**). The most frequently reported adverse events included weight gain, insomnia, increased appetite, and mood swings with prednisone and nausea, fatigue, any abnormal liver-function tests, and abdominal pain with methotrexate.

The mean change in weight was 5.0±5.1 kg in the prednisone group and 1.1±4.0 kg in the methotrexate group. The mean change in waist circumference was 4.4±6.6 cm in the prednisone group and 0.5±4.9 cm in the methotrexate group.

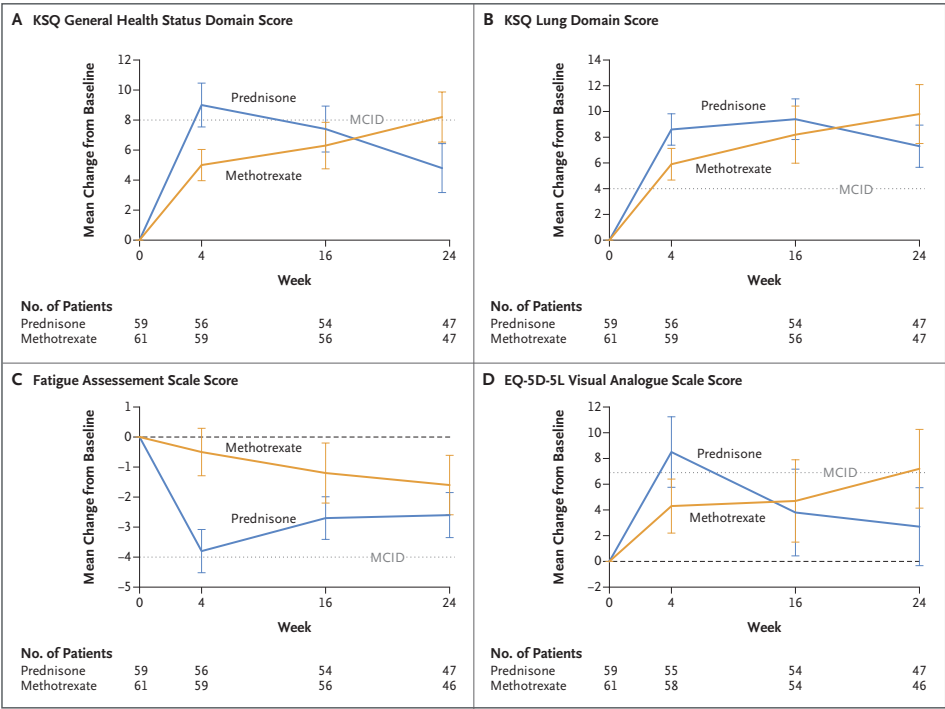


Figure 2. Change in Patient-Reported Outcomes (Modified Intention-to-Treat Analysis). Shown are the mean changes from baseline in the King's Sarcoidosis Questionnaire (KSQ) general health status domain score (range, 0 to 100; higher scores indicate better health status) (Panel A), the KSQ lung domain score (range, 0 to 100; higher scores indicate fewer symptoms) (Panel B), the Fatigue Assessment Scale score (range, 10 to 50; higher scores indicate worse fatigue) (Panel C), and the EuroQol Group 5-Dimension 5-Level (EQ-5D-5L) visual analogue scale score (range, 0 to 100; higher scores indicate better health status) (Panel D). Because the minimal clinically important difference (MCID) for sarcoidosis as assessed with the EQ-5D-5L visual analogue scale is unknown, the minimal clinically important difference for chronic obstructive pulmonary disease is shown. I bars indicate 95% confidence intervals.

Discussion

This multicenter, randomized trial assessed the efficacy of methotrexate as compared with prednisone as first-line treatment for pulmonary sarcoidosis. Methotrexate was noninferior to prednisone regarding the change in the percentage of the predicted FVC between baseline and week 24.

The need for alternative first-line treatment options for pulmonary sarcoidosis has been recognized for many years; however, evidence from randomized, controlled trials of alternative treatments was lacking. In the current trial, we have shown that methotrexate may be an alternative to prednisone as first-line treatment in patients with pulmonary sarcoidosis. In our trial, prednisone led to a rapid increase in the percentage of the predicted FVC within 4 weeks, after which this value remained stable through week 24. This finding is in line with results of previous trials, in which major improvement in pulmonary function was found to occur within 1 month after starting prednisone (28-30). The improvement from baseline in the percentage of the predicted FVC was more gradual with methotrexate than with prednisone, but the change between baseline and week 24 was similar in the two groups. In both treatment groups, the changes at week 24 in the KSQ lung domain score and general health status domain score, EQ-5D-5L VAS score, and FAS score showed a pattern generally similar to that of the changes at week 24 in the percentage of the predicted FVC (**Figure 2**).

The current trial included patients with a wide range of disease severity (34% to 125% of the predicted FVC). We did not observe a substantial difference between the prednisone and methotrexate groups in the percentages of patients who had treatment failure, needed rescue therapy, or withdrew from the trial. The lack of a difference in these percentages is reassuring because one of the hesitations for the use of methotrexate as first-line treatment has been an onset of action that is slower than that for prednisone (31). The recently published SARCORT trial showed that 45% of patients who received 6 months of prednisone treatment for pulmonary sarcoidosis had disease relapse between 12 and 18 months after the cessation of therapy.³² Thus, long-term treatment of sarcoidosis is likely to be needed in order to adequately suppress granulomatous inflammation, which means that the side-effect profile and patient preference are key issues for adherence (32). In patients with severe symptoms or impaired pulmonary function, methotrexate combined with short-term use of prednisone could be considered as initial treatment, but such an approach warrants further study.

The total number of adverse events was similar in the trial groups, but the adverse-event profiles of prednisone and methotrexate were clearly different. The percentage of adverse events that were transient (i.e., not ongoing at week 24) was higher in the methotrexate group than in the prednisone group (63% vs. 46%). One of the reasons for this finding could be that changes in the route of methotrexate administration or the methotrexate dose were successful in alleviating adverse events.

Elevated liver-enzyme levels were seen in 25% of the patients treated with methotrexate, with the alanine aminotransferase level being more than three times the upper limit of the normal range in 9% of the patients and leading to treatment discontinuation in two patients. This aligns with findings from methotrexate studies involving patients with rheumatoid arthritis (33,34). Longterm use of methotrexate in patients with rheumatoid arthritis is also associated with increased liver-enzyme levels and toxic effects; data in previous studies on the risk of liver fibrosis and cirrhosis are inconsistent (34).

Increases of 5.0 kg in weight and 4.4 cm in waist circumference were observed at week 24 in the prednisone group and persisted after the prednisone dose was tapered; these findings are similar to those in previous trials.^{10,32} Long-term use of prednisone is associated with a high risk of chronic conditions, such as hypertension and diabetes mellitus, with waist circumference and body-mass index as direct risk factors (35-38).

Three treatment-related serious adverse events were reported in the methotrexate group as compared with one in the prednisone group. The small number of events precludes definitive conclusions about the clinical implications of this finding. Differences between methotrexate and prednisone regarding the onset of action and adverse-event profile provide important information to guide shared decision making between patients and providers in choosing the most appropriate treatment.

The current trial was designed before the most recent treatment guidelines for sarcoidosis were published.⁴ As a result, in our trial the initial prednisone dose of 40 mg per day differs from the current guideline-recommended dose of 20 to 40 mg per day, and the initial methotrexate dose of 15 mg per week (which was increased to 25 mg per week if the side-effect profile was acceptable) differs from the current guideline-recommended dose of 10 to 15 mg per week (4). However, the current guideline recommendations are based on low to very low quality of

evidence, and future studies are needed to clarify the best dose and frequency of administration (4). The SARCORT trial showed that the effects of medium-dose prednisone (20 mg per day) were similar to those of high-dose prednisone (40 mg per day); nevertheless, the medium dose did not lead to a lower incidence of adverse events than the high dose (32). Methotrexate has been extensively investigated in patients with rheumatoid arthritis, and the appropriate dose is considered to be 20 to 25 mg per week (39). In patients with sarcoidosis, the appropriate methotrexate dose remains to be elucidated; a previous prospective study showed that a lack of methotrexate efficacy was mainly associated with a dose of 10 mg per week, a finding that appears to indicate the need for a dose of at least 15 mg per week (17).

Our trial has several limitations. Although this was a large randomized, controlled trial of first-line treatment in sarcoidosis, the trial was relatively small and conducted in a single country. The number of patients screened for inclusion in the trial was not consistently reported in all centers, and the effect that this may have had on the generalizability of the results is unknown. Nonadherence to the treatment schedule (i.e., crossover to the other treatment group) could have biased the results of the modified intention-to-treat analysis toward noninferiority; however, our per-protocol analysis also showed noninferiority of methotrexate. Limitations in funding and the need for treatment schedules for two drugs, including schedules for dose increases and decreases, precluded blinding.

In patients with pulmonary sarcoidosis, initial treatment with methotrexate was noninferior to that with prednisone regarding the change from baseline to week 24 in the percentage of the predicted FVC. Differences in the side-effect profile and time to onset of action between prednisone and methotrexate may inform shared decision making by patients and providers about the appropriate treatment approach.

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Supplementary appendix

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Vivienne Kahlmann¹, Montse Janssen Bonás², Catharina C. Moor¹, Jan C. Grutters^{2,3}, Rémy L.M. Mostard^{4,5}, Henricus N.A.J. van Rijswijk⁶, Jan van der Maten⁷, Emiel R. Marges⁸, Linda A.A. Moonen⁹, Maria J. Overbeek^{8,10}, Bart Koopman¹¹, Daan W. Loth¹², Esther J. Nossent¹³, Michiel Wagenaar¹⁴, Henk Kramer¹⁵, Pascal L.M.L. Wielders¹⁶, Peter I. Bonta¹⁷, Stefan Walen¹⁸, Brigitte A.H.A. Bogaarts¹⁹, René Kerstens²⁰, Mayka Overgaauw²¹, Marcel Veltkamp^{2,3}, and Marlies S. Wijzenbeek¹, and PREDMETH collaborators

1.Center of Excellence for Interstitial Lung Diseases and Sarcoidosis (member of the European Reference Network on Rare Respiratory Diseases), Department of Respiratory Medicine, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, the Netherlands; 2. Interstitial Lung Disease Center of Excellence (member of the European Reference Network on Rare Respiratory Diseases), St. Antonius Hospital, Nieuwegein, the Netherlands; 3. Division of Heart and Lungs, University Medical Center, Utrecht, the Netherlands; 4. Department of Respiratory Medicine, Zuyderland Medical Center, Heerlen, the Netherlands; 5. Department of Respiratory Medicine, Maastricht University Medical Center, Maastricht, the Netherlands; 6. Department of Pulmonary Medicine, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands; 7. Department of Pulmonary Diseases, Medical Center Leeuwarden, Leeuwarden, the Netherlands; 8. Department of Pulmonary Medicine, Leiden University Medical Center, Leiden, the Netherlands; 9. Department of Pulmonary Medicine, Rijnstate Hospital, Arnhem, the Netherlands; 10. Department of Pulmonary Medicine, Haaglanden Medical Center, the Hague, the Netherlands; 11. Department of Pulmonary Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam; 12. Department of Pulmonary Medicine, Amphia, Breda, the Netherlands; 13. Center of Expertise for Interstitial Lung Disease and Sarcoidosis, Department of Pulmonary Medicine, Amsterdam University Medical Center, Amsterdam; 14. Department of Pulmonary Medicine, Medisch Spectrum Twente, Enschede, the Netherlands; 15. Department of Pulmonary Medicine, Martini Hospital, Groningen, the Netherlands; 16. Department of Pulmonary Medicine, Catharina Hospital, Eindhoven, the Netherlands; 17. Center of Expertise for Interstitial Lung Disease and Sarcoidosis, Department of Pulmonary Medicine, Amsterdam University Medical Center, Amsterdam; 18. Department of Pulmonary Medicine, Isala Hospital, Zwolle, the Netherlands; 19. Department of Pulmonary Diseases, VieCuri Medical Center, Venlo, the Netherlands; 20. Orion Statistical Consulting, Hilvarenbeek, the Netherlands; 21. Sarcoidosis Patient Association, Alkmaar, the Netherlands.

Section S1. Steering committee, patient panel, and PREDMETH collaborators

Steering committee	
Vivienne Kahlmann	Center of Excellence for Interstitial Lung Diseases and Sarcoidosis, member of the European Reference Network Lung, Department of Respiratory Medicine, Erasmus Medical Center, University Medical Center Rotterdam, the Netherlands
Montse Janssen Bonás	Interstitial Lung Diseases Center of Excellence, member of the European Reference Network Lung, St. Antonius Hospital, Nieuwegein, the Netherlands
Catharina C. Moor	Center of Excellence for Interstitial Lung Diseases and Sarcoidosis, member of the European Reference Network Lung, Department of Respiratory Medicine, Erasmus Medical Center, University Medical Center Rotterdam, the Netherlands
Marcel Veltkamp	Interstitial Lung Diseases Center of Excellence, member of the European Reference Network Lung, St. Antonius Hospital, Nieuwegein, the Netherlands Division of Heart and Lungs, University Medical Center, Utrecht, the Netherlands
Marlies S. Wijsenbeek	Center of Excellence for Interstitial Lung Diseases and Sarcoidosis, member of the European Reference Network Lung, Department of Respiratory Medicine, Erasmus Medical Center, University Medical Center Rotterdam, the Netherlands
Patient panel	
Mayka Overgaauw	Sarcoidosis patient association, Sarcoidose.nl, Alkmaar, the Netherlands
Gerrit Vruwink	Sarcoidosis patient association, Sarcoidose.nl, Alkmaar, the Netherlands
Anton Berendse	Sarcoidosis patient association, Sarcoidose.nl, Alkmaar, the Netherlands
PREDMETH collaborators	
F.T. van Beek	Interstitial Lung Diseases Center of Excellence, member of the European Reference Network Lung, St. Antonius Hospital, Nieuwegein, the Netherlands
J.M.W. van den Berg	Department of Pulmonology, Haga Teaching Hospital, The Hague, The Netherlands
B.G. Boerrigter	Center of expertise for Interstitial Lung Disease and Sarcoidosis, Department of Pulmonary Medicine, Amsterdam UMC, location VUmc, Amsterdam, the Netherlands
P. Bresser	Department of Pulmonary Medicine, OLVG, Amsterdam, the Netherlands

Section S1. Continued

M. Bülbül	Department of Pulmonary Medicine, Central Military Hospital, Utrecht, the Netherlands
P.P. Chandoesing	Center of Excellence for Interstitial Lung Diseases and Sarcoidosis, member of the European Reference Network Lung, Department of Respiratory Medicine, Erasmus Medical Center, University Medical Center Rotterdam, the Netherlands
S.M. Collard	Department of Pulmonary Medicine, Meander Medical Center, Amersfoort, the Netherlands
F.L.J. Custers	Department of Respiratory Medicine, Zuyderland Medical Center, Heerlen, the Netherlands
M.G. de Gier	Department of Pulmonary Medicine, Tergooi Medical Center, Hilversum, Netherlands
M.J.J.H. Grootenboers	Department of Pulmonary Medicine, Amphia, Breda, The Netherlands
G. Helfrich	Department of Pulmonary Diseases, Maasstad Hospital, Rotterdam, The Netherlands.
P. Hendriks	Department of Pulmonary Medicine, Isala, Zwolle, the Netherlands
J.C. Kuijvenhoven-Varkevisser	Department of Pulmonary Diseases, Medical Center Leeuwarden, The Netherlands
M. van Laren	Department of Pulmonary Medicine, Dijklander Ziekenhuis locatie Hoorn en Purmerend
G.J.M. Limonard	Department of Pulmonary Medicine, Diaconessenhuis, Utrecht, the Netherlands
C.J. van Loenhout,	Department of pulmonary medicine, Bravis hospital, Bergen op Zoom, the Netherlands
J.R. Miedema	Center of Excellence for Interstitial Lung Diseases and Sarcoidosis, member of the European Reference Network Lung, Department of Respiratory Medicine, Erasmus Medical Center, University Medical Center Rotterdam, the Netherlands
M.M. Nagtegaal	Department of pulmonology, Groene Hart Ziekenhuis, Gouda, the Netherlands
S.F.M. Nijman	Center of expertise for Interstitial Lung Disease and Sarcoidosis, Department of Pulmonary Medicine, Amsterdam UMC, location VUmc, Amsterdam, the Netherlands
M.J.R. Quanjel	Interstitial Lung Diseases Center of Excellence, member of the European Reference Network Lung, St. Antonius Hospital, Nieuwegein, the Netherlands
E.L. Schakenraad	Department of Pulmonary Medicine, Catharina Hospital, Eindhoven, the Netherlands

Section S1. Continued

C.A. van der Sloot	Department of Pulmonary Medicine, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands
J.P.M. van der Valk	Department of pulmonary medicine, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands
M.J.T. van de Ven	Department of Pulmonary Medicine, Rijnstate Hospital, Arnhem, the Netherlands
A.D.M. Vorselaars	Division of Heart and Lungs, University Medical Center, Utrecht, the Netherlands

Table S1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Diagnosis of sarcoidosis according to the ATS/ERS/WASOG criteria (1), in case of absent histology a diagnosis of sarcoidosis can also be established in a multidisciplinary team meeting in a sarcoidosis expert center based on a highly suggestive clinical and radiological picture • Age ≥18 years • A pulmonary indication for treatment and parenchymal involvement on X-ray or chest CT-scan conducted within three months before inclusion (determined by the treating physician and according to current guidelines) • A forced vital capacity (FVC) of ≤90% of predicted, or a diffusion capacity of the lung for carbon monoxide (DLCO) ≤70% of predicted, or an absolute decline of ≥5% FVC, or an absolute ≥10% DLCO decline in the past year	• Any condition or circumstance that, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study procedures • Previous immunosuppressive treatment for sarcoidosis • Use of systemic immunosuppressive therapy within the preceding three months for another disease than sarcoidosis • Pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study treatment or within 90 days after the last dose in the randomized study phase. For males; planning to pro-create during the study or within 90 days after the last dose of the randomized study phase • Primary systemic treatment indication being an extra pulmonary location of sarcoidosis (e.g. cardiac or neurological) • Contra-indication for methotrexate or corticosteroids*

*Contra-indications for methotrexate or corticosteroids are defined as: severely impaired renal function (creatinine clearance <30 ml/min), impaired hepatic function (serum bilirubin-value >5 mg/dl or 85,5 micromole/l), bone marrow insufficiency with severe leukopenia, thrombocytopenia, or anemia, severe acute or chronic infections, such as tuberculosis, human immunodeficiency virus, parasitic infections or other immunodeficiency syndromes, mouth, stomach or duodenal ulcers.

Table S2. Patient-reported outcome measurements

Questionnaire	Description	MCID
King's sarcoidosis Questionnaire (KSQ) (2-4)	- Validated questionnaire to assess health status in patients with sarcoidosis 29 items in five subdomains (General Health Status, Lung, Eyes, Skin, and Medication) - Scores ranging from 0-100, higher scores representing better health status	MCID for KSQ General Health status is 8 points and for KSQ Lung 4 points
Fatigue assessment scale (FAS) (5, 6)	- Validated questionnaire to assess fatigue in patients with sarcoidosis. 10 questions answered on a 5-point Likert scale - Scores range from 10-50 points, with a score ≥ 22 as cut-off for fatigue	The MCID is 4 points or a difference of $\geq 10\%$
The EuroQol five dimensions 5-level questionnaire (EQ-5D-5L) (7)	- Standardized instrument to measure health outcomes - Two components: health description (five dimensions) and valuation (visual analogue scale from 0 to 100).	- The MCID in sarcoidosis is currently unknown - The MCID in COPD for the EQ-5D-5L health description (index score) and VAS score, are respectively 0.051 and 6.9
Patient experiences and satisfaction with medication (PESAM) questionnaire	- The expectations module includes 11 items rated on 0-4 Likert Scale (negative to positive). - The experiences module includes 18 items in three domains (effectiveness, side effects and ease of use). Patient experiences are scores on a 0-4 Likert scale (higher score indicate more positive experiences. Satisfaction is scored from -5 to 5. Finally, patients scored how important they considered side effects, and ease of use were rated on 0-4 Likert scale.	The MCID is not known

COPD = chronic obstructive lung disease
The patient-reported outcomes were collected via an online CE-marked secured application (Curavista, the Netherlands). MCID = minimal clinical important difference. Patients also filled out the chronic respiratory questionnaire. As there were technical issues with saving and extracting the CRQ data in the platform, we could not include this questionnaire.

Table S3. Representativeness of study participants of the PREDMETH trial

Category	
Disease under investigation	Pulmonary sarcoidosis
Sex and gender	Men and women are equally affected
Age	The average age onset is 40-50 years of age, with a younger peak age in men (30-50 years) compared to women (50-60 years).
Geography	The incidence and prevalence of sarcoidosis varies greatly depending on the regions across the world. Prevalence is highest in Sweden and Canada (140-160 per 100.000) and is the lowest in Asian countries like Korea and Japan (1-5 per 100.000).
Race or ethnic group	Sarcoidosis is prevalent in all ethnic groups. The prevalence in African Americans is higher compared to Caucasians and their prognosis is less favorable. The prevalence in Hispanics is approximately half of the Caucasian population and slightly higher compared to the Asian population.
Other considerations	Sarcoidosis is a very heterogeneous disease in clinical presentation and severity. As sarcoidosis can share clinical, radiological and histopathological similarities, the exact prevalence of pulmonary sarcoidosis in tuberculosis-endemic countries is not known.
Overall representativeness of this trial	The study population in this trial was mainly Caucasian (85%), resulting from the Dutch population composition together with requirement to read and understand the Dutch language. Therefore, Black, Hispanic and Asian patients are under-represented in this trial. The participants did not demonstrate the expected 1:1 ratio of men and women, with male sex being overrepresented in this trial, we do not have a clear explanation for this.

References: (8-10)

Tables S4. Within and between group change in forced vital capacity

Table S4.1. Within and between-group change in FVC in the intention to treat population

Visit		Methotrexate (n=68)		Methotrexate (n=68) Change		Prednisone (n=69)	Prednisone (n=69) Change	Difference LS means (95%CI)	
Baseline	n	68				69			
	Mean	74.8				79.8			
	SE	1.54				1.86			
	Median	76.0				79.0			
	Q1;Q3	(69.0;82.8)				(71.0;87.0)			
	Min;max	(35.8;108.0)				(34.4;125.4)			
Week 4	n	68	68			69	69		
	Mean	76.7	1.9			86.2	6.4	-5.11 (-7.19;-3.04)	
	SE	1.50	0.51			1.86	0.92		
	Median	77.6	1.8			88.0	6.0		
	Q1;Q3	(68.0;84.0)	(-1.0;5.0)			(76.0;96.0)	(2.0;10.3)		
	Min;max	(37.6;112.0)	(-7.0;16.0)			(43.1;135.6)	(-11.0;38.0)		
Week 16	n	59	59			64	64		
	Mean	80.0	4.8			87.1	7.8	-4.09 (-6.99;-1.18)	
	SE	1.69	1.15			1.83	1.09		
	Median	81.0	4.0			87.2	7.5		
	Q1;Q3	(72.0;88.0)	(-1.0;8.8)			(76.0;94.6)	(2.0;13.0)		
	Min;max	(42.0;113.0)	(-11.0;33.0)			(45.3;122.4)	(-15.0;30.0)		
Week 24	n	67	67			68	68		
	Mean	81.0	6.1			86.6	6.7	-1.17 (-4.27; 1.93)	
	SE	1.62	1.20			1.77	1.12		
	Median	80.2	5.0			85.0	6.5		
	Q1;Q3	(73.0;89.0)	(0.0;11.0)			(76.5;95.7)	(1.1;13.9)		
	Min;max	(48.2;111.0)	(-21.0;44.0)			(46.8;127.0)	(-15.0;27.6)		

Difference and 95% confidence intervals (CI) are based on a mixed model of repeated measurements including treatment and baseline value.

FVC = forced vital capacity, SE = standard error, LS = least squares

Table S4.2. Within and between-group change in FVC in the per protocol population

Visit		Methotrexate (n=54)	Methotrexate (n=54) Change	Prednisone (n=58)	Prednisone (n=58) Change	Difference LS means (95%CI)
Baseline	n	54		58		
	Mean	75.2		79.5		
	SE	1.65		2.09		
	Median	76.0		79.0		
	Q1;Q3	(69.0;81.0)		(67.0;88.0)		
	Min;max	(35.8;108.0)		(34.4;125.4)		
Week 4	n	54	54	58	58	
	Mean	77.3	2.1	86.5	7.0	-5.32 (-7.53;-3.10)
	SE	1.59	0.58	2.14	0.94	
	Median	78.0	1.8	88.0	7.0	
	Q1;Q3	(69.0;84.0)	(-1.1;5.0)	(76.0;97.0)	(2.0;10.3)	
	Min;max	(37.6;112.0)	(-7.0;16.0)	(43.1;135.6)	(-11.0;38.0)	
Week 16	n	49	49	54	54	
	Mean	80.5	5.2	87.6	8.7	-4.21 (-7.31;-1.11)
	SE	1.83	1.18	2.09	1.13	
	Median	81.0	6.0	89.0	8.0	
	Q1;Q3	(73.0;88.0)	(0.0;8.0)	(76.0;95.3)	(2.3;13.3)	
	Min;max	(42.0;113.0)	(-11.0;33.0)	(45.3;122.4)	(-8.0;30.0)	
Week 24	n	54	54	58	58	
	Mean	81.8	6.6	87.1	7.5	-1.40 (-4.85; 2.05)
	SE	1.83	1.37	2.01	1.18	
	Median	80.6	5.0	85.5	7.9	
	Q1;Q3	(74.0;90.0)	(0.4;11.0)	(77.0;97.0)	(2.0;15.0)	
	Min;max	(48.2;111.0)	(-21.0;44.0)	(46.8;127.0)	(-14.9;27.6)	

Difference and 95% confidence intervals (CI) are based on a mixed model of repeated measurements including treatment and baseline value.

FVC = forced vital capacity, LS = least squares, SE = standard error

Tables S5. Medication dosing over time

Table S5.1 Medication exposure up to week 24 in the per protocol population

Parameter	Prednisone (n=58)	Methotrexate (n=54)
Average daily dose (mg)	21.1±2.1	20.1 ± 3.0
Total dose	3368.9±455.6	421.4±135.0

Data are presented as mean and standard deviation.

Tables S5.2 Medication at week 24

Table S5.2.1 Prednisone dose at week 24 in the intention to treat population

Prednisone dose (mg/day)	Number of patients (%)
0	2 (2.9%)
5	5 (7.4%)
7,5	4 (5.9%)
10	52 (76.5%)
15	4 (5.9%)
20	1 (1.5%)

Table S5.2.2. Prednisone dose at week 24 in the per protocol population

Prednisone dose (mg/day)	Number of patients (%)
5	3 (5%)
7,5	3 (5%)
10	51 (88%)
15	1 (2%)

Table S5.2.3. Methotrexate dose at week 24 in the intention to treat population

Methotrexate dose (mg/week)	Number of patients (%)			
	Oral	Subcutaneous	Dose dived	Total
0				7 (10%)
10	3	1	0	4 (15%)
12,5	2	0	0	2 (3%)
15	7	2	1	10 (15%)
20	18	2	3	23 (34%)
25	19	2	0	21 (31%)

Table S5.2.4. Methotrexate dose at week 24 in the per protocol population

Methotrexate dose (mg/week)	Number of patients (%)			
	Oral	Subcutaneous	Dose dived	Total
10	1	1	0	2 (4%)
12,5	2	0	0	2 (4%)
15	5	2	1	8 (14%)
20	16	2	3	22 (40%)
25	19	2	0	21 (38%)

Tables S6. Within group change and between group difference in change in patient-reported outcomes

Table S6.1. KSQ – General Health

Visit		Methotrexate (n=68)		Methotrexate (n=68) Change		Prednisone (n=69)	Prednisone (n=69) Change	Difference LS means (95%CI)	
Baseline	n	61				59			
	Mean	59.4				63.3			
	SE	1.73				1.72			
Week 4	n	65		59		64	56		
	Mean	64.9		5.0		71.9	9.0	-5.20 (-8.61;-1.80)	
	SE	1.59		1.04		1.99	1.46		
Week 16	n	60		56		59	54		
	Mean	66.1		6.3		70.8	7.4	-2.21 (-6.26; 1.84)	
	SE	1.63		1.55		1.99	1.53		
Week 24	n	51		47		54	47		
	Mean	69.1		8.2		69.0	4.8	2.50 (-1.88; 6.88)	
	SE	1.94		1.67		2.08	1.63		

Difference and 95% confidence intervals (CI) are based on a mixed model of repeated measurements including treatment and baseline value.

KSQ = Kings sarcoidosis Questionnaire, LS = least squares, SE = standard error
** As we did not account for multiplicity, the Cis cannot be used for inference.

Table S6.2. KSQ – LUNG

Visit		Methotrexate (n=68)		Methotrexate (n=68) Change		Prednisone (n=69)	Prednisone (n=69) Change	Difference LS means (95%CI)	
Baseline	n	61				59			
	Mean	59.4				60.5			
	SE	1.93				1.88			
Week 4	n	65		59		64	56		
	Mean	65.2		5.9		68.1	8.6	-2.99 (-6.27; 0.28)	
	SE	1.82		1.23		2.02	1.22		
Week 16	n	60		56		59	54		
	Mean	67.9		8.2		70.6	9.4	-1.23 (-6.33;3.87)	
	SE	2.02		2.22		2.13	1.58		
Week 24	n	51		47		54	47		
	Mean	69.8		9.8		68.6	7.3	2.88 (-2.20; 7.97)	
	SE	2.08		2.29		2.30	1.64		

LS difference and 95% confidence intervals (CI) are based on a mixed model of repeated measurements with including treatment and baseline value.

KSQ = Kings sarcoidosis Questionnaire, LS = least squares, SE = standard error.
** As we did not account for multiplicity, the Cis cannot be used for inference.

Table S6.3. Fatigue assessment scale

Visit		Methotrexate (n=68)	Methotrexate (n=68) Change	Prednisone (n=69)	Prednisone (n=69) Change	Difference LS means (95%CI)
Baseline	n	61		59		
	Mean	25.9		25.1		
	SE	1.06		1.06		
Week 4	n	65	59	64	56	
	Mean	25.2	-0.5	21.4	-3.8	3.68 (1.78;5.58)
	SE	0.98	0.79	0.91	0.72	
Week 16	n	59	55	59	54	
	Mean	24.0	-1.2	21.7	-2.7	1.63 (-0.61; 3.87)
	SE	1.02	1.0	1.04	0.71	
Week 24	n	50	46	54	47	
	Mean	23.7	-1.6	21.6	-2.6	1.41 (-0.79; 3.61)
	SE	1.07	0.99	1.04	0.75	

*Difference and 95% confidence intervals (CI) are based on a mixed model of repeated measurements with including treatment and baseline value.

LS = least squares, SE = standard error

** As we did not account for multiplicity, the Cis cannot be used for inference.

Table S6.4. EQ-5D-5L health description index score

Visit		Methotrexate (n=68)	Methotrexate (n=68) Change	Prednisone (n=69)	Prednisone (n=69) Change	Difference LS means (95%CI)
Baseline	n	60		59		
	Mean	0.72		0.77		
	SE	0.02		0.03		
Week 4	n	65	58	63	55	
	Mean	0.76	0.02	0.83	0.08	-0.07 (-0.12;-0.02)
	SE	0.02	0.02	0.02	0.02	
Week 16	n	59	54	59	54	
	Mean	0.80	0.05	0.82	0.04	0.00 (-0.05;0.06)
	SE	0.02	0.02	0.03	0.03	
Week 24	n	49	46	54	47	
	Mean	0.80	0.06	0.82	0.04	0.01 (-0.05;0.06)
	SE	0.02	0.03	0.02	0.02	

*Difference and 95% confidence intervals (CI) are based on a mixed model of repeated measurements including treatment and baseline value. EQ-5D-5L = EuroQol five dimensions 5-level questionnaire,

LS = least squares, SE = standard error

** As we did not account for multiplicity, the Cis cannot be used for inference.

Table S6.5. EQ-5D VAS SCORE

Visit		Methotrexate (n=68)	Methotrexate (n=68) Change	Prednisone (n=69)	Prednisone (n=69) Change	Difference LS means (95%CI)
Baseline	n	60		59		
	Mean	60.6		65.1		
	SE	2.61		2.84		
Week 4	n	65	58	63	55	
	Mean	64.8	4.3	72.4	8.5	-6.19 (-12.0;-0.39)
	SE	2.49	2.10	2.41	2.74	
Week 16	n	59	54	59	54	
	Mean	67.5	4.7	69.6	3.8	-1.63 (-9.49;6.24)
	SE	2.76	3.20	2.81	3.37	
Week 24	n	49	46	54	47	-1.49 (-8.66; 5.68)
	Mean	68.7	7.2	69.4	2.7	
	SE	2.60	3.06	2.99	3.03	

*Difference and 95% confidence intervals (CI) are based on a mixed model of repeated measurements including treatment and baseline value. EQ-5D VAS = EuroQol five dimensions Visual Analog Scale,

LS = least squares, SE = standard error.
** As we did not account for multiplicity, the CIs cannot be used for inference.

Table S7. Patient experiences and satisfaction with medication at week 24 (ITT population)*

	Prednisone (n=69)	Methotrexate (n=68)
Experiences		
Effectiveness	1.9 (1.0); n=47	1.8(1.1); n=48
Side effects	3.2 (0.0); n=54	3.2 (0.8); n=46
Ease of use	3.8 (0.4); n=54	3.8 (0.4); n=50
Satisfaction		
Effectiveness	2.0 (2.0); n=54	1.7 (2.1); n=50
Side effects	1.8 (2.0); n=42	1.4 (2.0); n=34
Ease of use	3.5 (1.2); n=54	3.5 (1.3); n=50
Overall satisfaction	2.3 (2.0); n=54	2.3 (2.0); n=50
Importance		
Effectiveness	3.7 (0.7) n=54	3.5 (0.9); n=50
Side effects	2.7 (1.0); n=54	2.6 (1.0); n=50
Ease of use	2.2 (1.3); n=54	2.0 (1.0); n=50

Data are presented as mean (SD).
*Number of patients is variable as patients had the option to fill out “don't know”.
The expectations module includes 11 items rated on 0-4 Likert Scale (negative to positive).
The experiences module includes 18 items; experiences and importance were rated on 0-4 Likert scale; satisfaction from -5 to 5, with higher scores indicating better satisfaction.

Tables S8. Reasons that led to treatment discontinuation, switch of medication, or non-adherence to the predefined treatment schedule

Table S8.1. Methotrexate group

Patient	Reason	Discontinuation of methotrexate	Adverse events
1	AE	Yes – switch to prednisone	Malaise
2	Progressive disease	No – lowering dose methotrexate and add on prednisone	X
3	AE	Yes – switch to prednisone	COVID-19
4	Cough	No – add on prednisone < 2 weeks due to cough	X
5	AE	Yes – switch to prednisone	Nausea, alopecia, palpitations
6	AE	Yes – no immunosuppressive medication after discontinuation of methotrexate	Liver test abnormalities
7	AE	Yes – switch to prednisone	Fatigue, nausea, vomiting, abdominal pain
8	AE	Yes – switch to prednisone (withdrew consent related to AE)	Headache, nausea, vomiting
9	Progressive disease	No - add on prednisone	X
10	Cough	No – add on prednisone < 2 weeks due to cough	X
11	Cough	No – add on prednisone < 2 weeks due to cough	X
12	AE	Yes – switch to prednisone	Liver test abnormalities
13	AE	Yes – switch to prednisone	Abdominal pain, fatigue
14	AE	Yes – switch to prednisone	Nausea, diarrhea

Table S8.2. Prednisone group

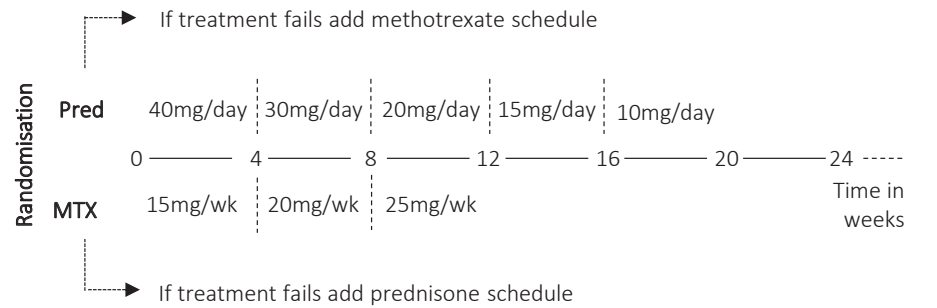
Patient	Reason	Discontinuation of prednisone	Adverse events
1	AE	No – lowering dose and add on methotrexate	Palpitations, sleep deprivation, agitation
2	AE	No – add on methotrexate	Diabetes mellitus, hypertension, weight increased
3	AE and progressive disease	No – lowering dose and add on methotrexate	Agitation, muscle cramps, cushingoid, insomnia, agitation
4	AE	No – add on methotrexate	Agitation, insomnia
5	AE and progressive disease	Yes – switch to methotrexate	Mood swings, nervousness, palpitations, dizziness, fatigue
6	Progressive disease	No – add on methotrexate	X
7	AE	Yes - no other immunosuppressive mediation (withdrew consent related to AE)	Hemolytic anemia treated with rituximab
8	AE	No – add on methotrexate	Hypertension
9	AE	Yes – no other immunosuppressive therapy after discontinuation of prednisone	Cushingoid, malaise, rash, insomnia, dizziness
10	AE	No – add on methotrexate	Headache, insomnia, mood swings, weight increased
11	AE	Yes – switch to methotrexate	Arthralgia, osteosclerosis, weight increased

Figures S1. Treatment schedules

*Our study protocol, provided as supplemental appendix to this manuscript, refers to prednisolone rather than prednisone. For clarification, prednisone was the used medication in this study.

Prednisone was initiated at 40mg per day and tapered every 4 weeks until a maintenance dose of 10mg per day at week 16. Patients received osteoporosis prophylaxis, calcium/ vitamin D and bisphosphonate, according to current clinical practice.

Methotrexate was initiated at 15mg per week and increased every 4 weeks with 5mg, to a maximum dose of 25mg per week if well tolerated. Patients received folic acid 5mg per week to prevent methotrexate related side effects. In case of side effects treatment adjustments could be made (e.g. reducing the dose or temporal discontinuation of treatment), according to a pre-defined protocol. If unacceptable side effects did not subside, patients could switch to the other treatment arm. In case of insufficient effectivity, defined as an absolute decline of $\geq 10\%$ predicted in FVC, the other treatment arm was added to the current treatment. In all situations, patients were asked to completed study visits.



*Pred = prednisone; MTX = methotrexate

Figure S1A. Standardized treatment schedule

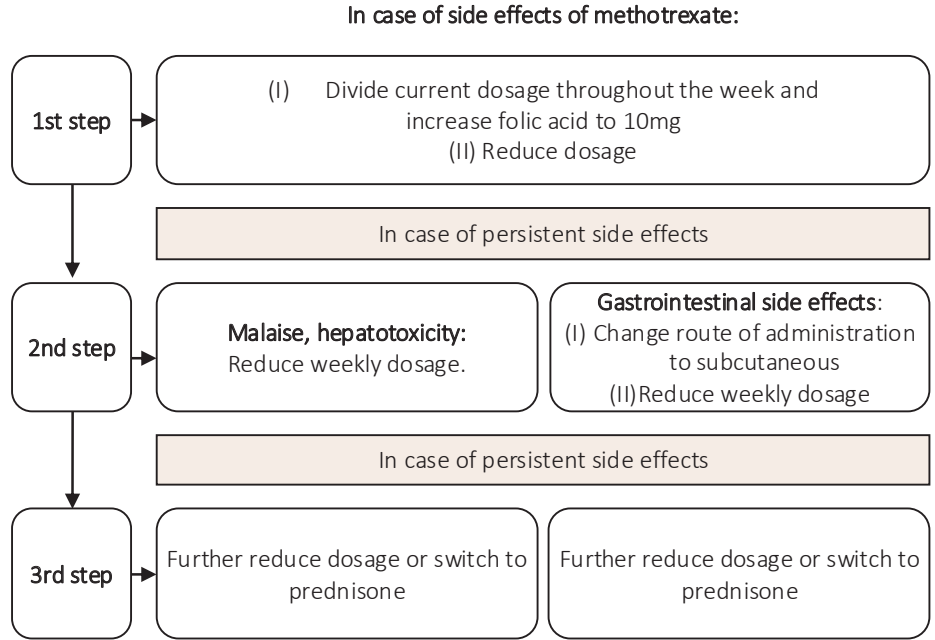


Figure S1B. Flowchart for adjustment of methotrexate treatment schedule in case of side effects

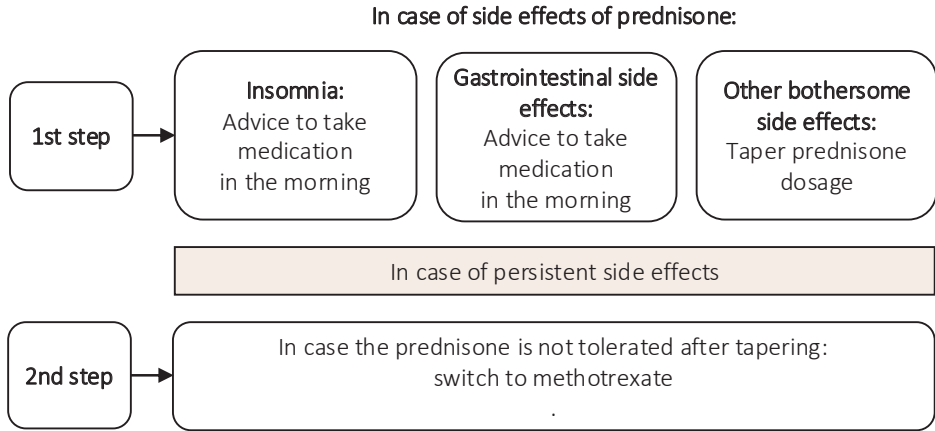


Figure S1C. Flowchart for adjustment of prednisone treatment schedule in case of side effects.

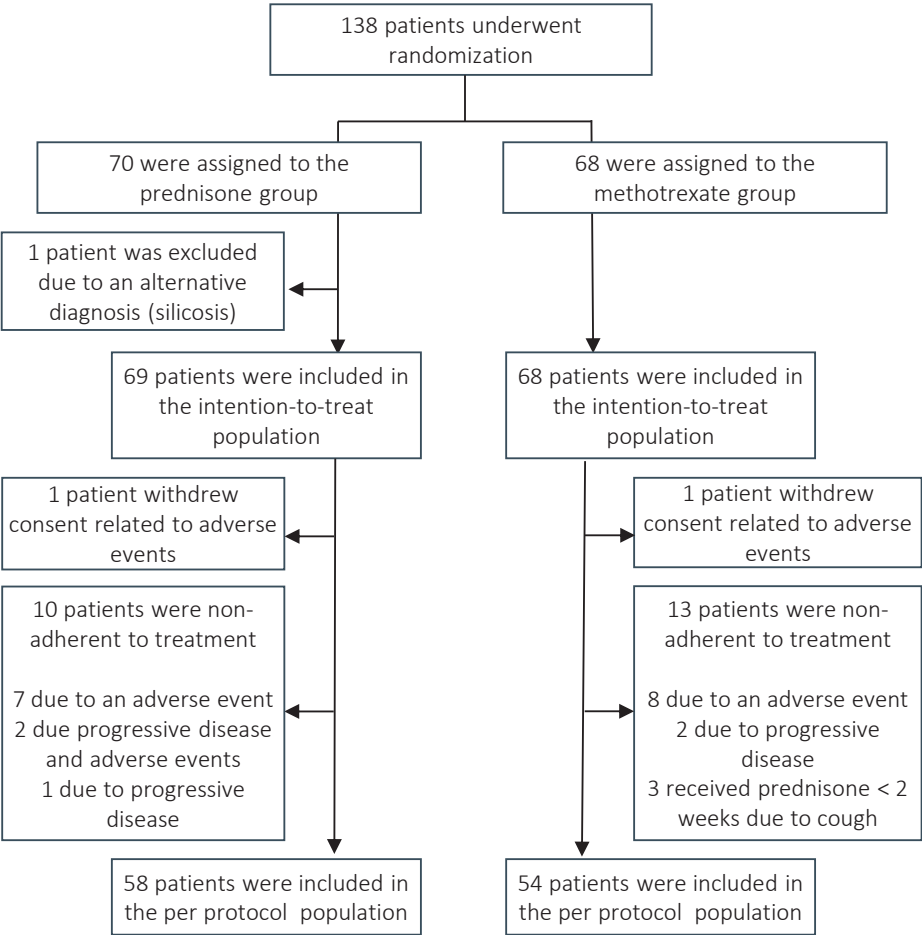


Figure S2. Study flowchart

*Non-adherence to treatment is defined as patients who switched to the other treatment arm or received the study treatment less than 80% of the time according to the predefined schedule.

Intention to treat population

135 patients were included in the modified intention to treat population.

Per protocol population

112 patients were included in the per protocol population. In the prednisone group, 1 patient withdrew consent and 10 patients were non-adherent to treatment: 7 patients due adverse events and 3 due to progressive disease. In the methotrexate group, 1 patient withdrew consent and 13 patients were non-adherent to treatment: 8 due to adverse events, and 2 due to progressive disease. Additionally, 3 patients received add-on prednisone <2 weeks due to persistent cough.

References of the supplementary appendix

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The background is an abstract composition of layered, torn paper and watercolor splatters. A large, light brown paper shape occupies the upper half, with smaller, darker brown and tan splatters scattered across it. Below this, a large, vibrant pinkish-red watercolor shape is prominent, with a darker red, textured shape partially visible underneath it on the left. In the bottom right corner, another red watercolor shape is partially visible. The overall effect is organic and artistic, with a focus on texture and color.

Part III

IMPROVING QUALITY OF
LIFE FOR PATIENTS
WITH SARCOIDOSIS

Chapter 8

Non-Organ Specific Manifestation of Sarcoidosis



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Vivienne Kahlmann, MD^{1*}; Divya C. Patel, DO^{2*}; Lucian T Marts, MD³;
Marlies S Wijsenbeek, MD PhD¹

*These authors share first authorship

1. Centre of Excellence for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
2. Division of Pulmonary, Critical Care and Sleep Medicine; University of Florida; Gainesville, FL
3. Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia

Abstract

Non-organ-specific manifestations such as fatigue, anxiety, depression, pain, cognitive dysfunction and small-fibre neuropathy are common in patients with sarcoidosis. These symptoms do not usually require immunosuppressive therapy and often persist, even while there are no signs of organ-specific sarcoidosis activity. These invisible manifestations of sarcoidosis often have a significant impact on health-related quality of life, and therefore should be adequately addressed and not be overlooked. In this chapter, we summarise the current literature about non-organ manifestations, including their prevalence, impact, assessment and treatment. Subsequently, we advocate a multidisciplinary and overarching approach for management and discuss future directions.

Introduction

The frequent invisible burden of sarcoidosis is predominantly caused by non-organ-specific manifestations of sarcoidosis such as fatigue, pain, cognitive dysfunction, anxiety, depression and small-fibre neuropathy (SFN) (**Figure 1**). The reported prevalence of these symptoms varies in the literature, but fatigue and pain in particular are reported in up to 60–90% of patients with sarcoidosis, although it should be realised that these numbers can be biased by the method and the population sampled (**Figure 2**) (1–14). These invisible and under-recognised manifestations of sarcoidosis have a major impact on the patient's and their family's wellbeing and directly impact health-related quality of life (HRQoL) (15) and can negatively impact social participation (16, 17). In the past decade, more value has been placed on patient-centred outcomes, which has led to increasing awareness and treatment trials for these manifestations.

In this chapter, we summarise the most recent insights on assessment and treatment of fatigue, pain, cognitive dysfunction, anxiety and depression in sarcoidosis, and propose a multidisciplinary and overarching management approach. We only briefly touch on SFN and HRQoL measurement, as these are discussed in detail elsewhere in this Monograph (18, 19). As the lack of good treatments for these invisible manifestations is unfortunately still a major frustration for patients and clinicians, we conclude with future directions and research needs.

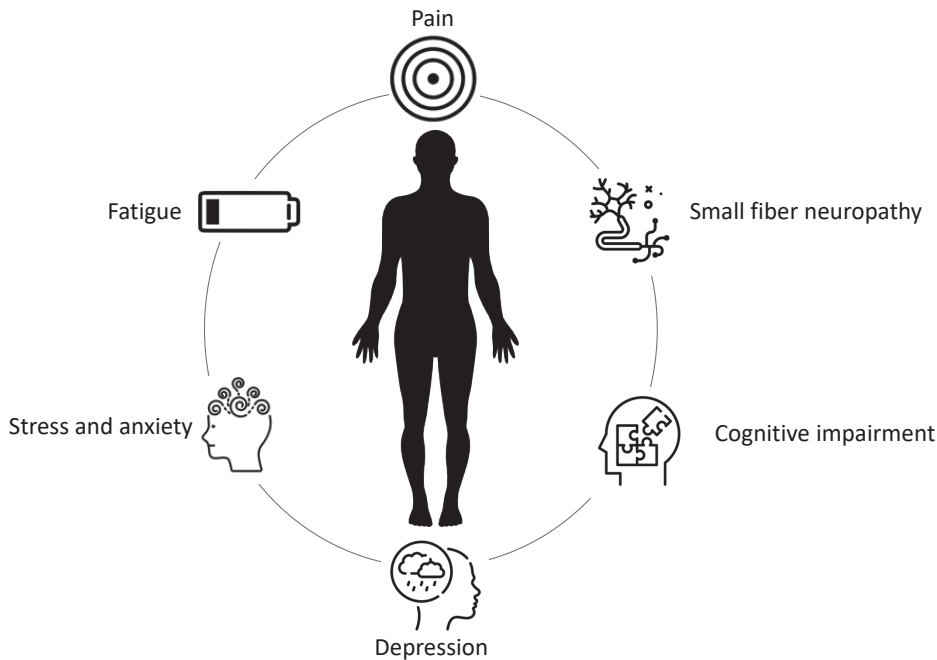


Figure 1. Non-organ manifestations of sarcoidosis include fatigue, pain, anxiety, depression, cognitive impairment and small-fibre neuropathy.

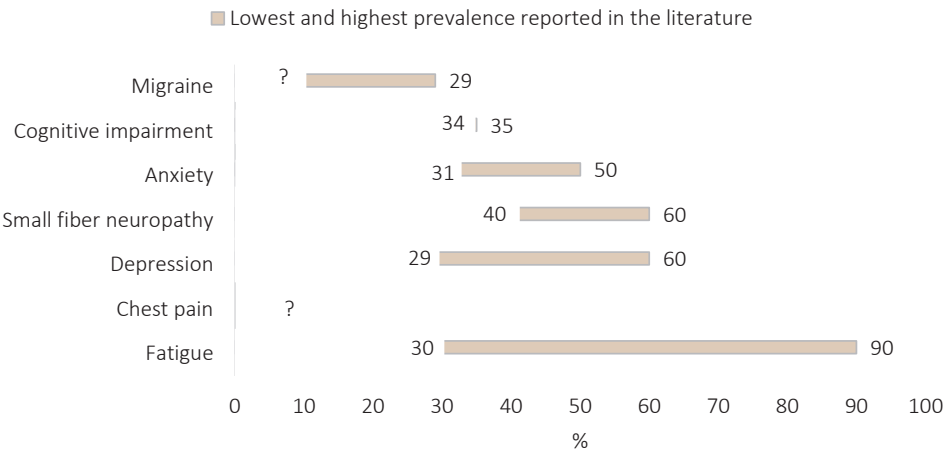


Figure 2. Prevalence of various non-organ manifestations of sarcoidosis represented as lowest and highest ranges reported in the medical literature. Note that prevalences vary and are influenced by many factors, including the population sampled.

Sarcoidosis-associated fatigue

Fatigue is a common and challenging symptom in patients with sarcoidosis, and often has a large impact on the lives of patients (1). There is no unambiguous definition of fatigue. It is usually described as a subjective symptom of lack of energy, tiredness, malaise and/or aversion to activity. Patients can experience limitations in physical and social functioning as well as work participation, and can be confronted with financial losses (20–22). Even when there are no signs of disease activity, fatigue is often present (23, 24). The challenge for patients and providers is that those suffering from fatigue often look completely healthy and therefore the consequences of fatigue can be easily underestimated (25). Remarkably, in a recent multinational patient survey, fatigue was reported in 90% of cases and extreme fatigue in 48% (1). In contrast, in the British Thoracic Society (BTS) sarcoidosis registry, a physician-reported registry, fatigue was only reported as a significant complaint in 30% of patients (26). This discrepancy between patient- and provider-reported outcomes emphasises the need for more awareness of fatigue. Management of fatigue is complicated due to incomplete understanding of the aetiology as well as multiple potential contributors to fatigue (27). Nevertheless, recognising patients with fatigue as well as identifying and treating underlying causes are necessary to improve care and quality of life for patients with sarcoidosis.

Assessment of fatigue

Patients should be asked regularly about the presence and impact of fatigue, as it can occur during all stages of sarcoidosis and often persists even while there are no signs of disease activity. Several patient-reported outcome measures (PROMs) have been developed to measure fatigue in sarcoidosis, such as the Fatigue Assessment Scale (FAS) and the Sarcoidosis Assessment Tool (SAT) fatigue subscale (Table 1) (30, 31, 45). If fatigue is present, an extensive patient history should be obtained. Multiple physical, psychological and behavioural factors may play a role in the development and persistence of fatigue, and each should be independently assessed, as management may differ depending on the underlying cause (Figure 3).

Physical factors

A structured approach is useful to assess causes of fatigue, starting with evaluation of the potentially opposing roles that immunosuppressive therapy may have in both the management and development of fatigue (Figure 4). Granulomatous inflammation can cause fatigue; in this case patients might

benefit from immunosuppressive therapy (46). Conversely, fatigue may be a side-effect of medication (47, 48). This is particularly true in the case of corticosteroid treatment (49, 50). Importantly, comorbidities that can trigger or aggravate fatigue must be excluded: additional blood tests might be required to exclude anaemia, hyperglycaemia, iron deficiency or a thyroid disorder.

Several studies have found that sleep disturbance was associated with higher levels of fatigue, cognitive dysfunction, depression and overall poorer HRQoL (51–53). Sleep disorders such as sleep disordered breathing or obstructive sleep apnoea (OSA), periodic limb movement disorder and restless legs syndrome are more prevalent in patients with sarcoidosis compared to healthy controls (54–56). Moreover, the use of corticosteroids can lead to weight gain, which increases the risk of developing OSA, and may worsen it (57). Patients can be screened for sleepiness using a validated questionnaire, for example the Epworth Sleepiness Scale, or OSA using the STOP-BANG (snoring, tiredness, observed apnoea, high blood pressure, body mass index, age, neck circumference and male gender) questionnaire (**Table 1**) (58). Since the diagnostic accuracy of these questionnaires is debatable, polysomnography could still be considered in patients with high clinical suspicion of OSA or in cases of severe unexplained fatigue. In a prospective cohort study, continuous positive airway pressure (CPAP) treatment had a positive impact on fatigue in patients with good CPAP compliance. As this was a single-arm study, these results need to be validated in future studies (33). Interestingly, adequate OSA treatment does not always seem to improve fatigue in patients with sarcoidosis (47). If fatigue persists despite adequate treatment of OSA, additional interventions could be considered and are addressed later in this section.

Fatigue is also associated with physical inactivity, dyspnoea and muscle weakness (42, 59–61). In addition to contributing to OSA, obesity in itself appears to have a negative effect on fatigue (62). Providers should regularly address the importance of physical activity and a healthy lifestyle (e.g. referral to a dietician and activity training) (63).

Psychological factors

Symptoms of anxiety and depression are common in sarcoidosis and have a bidirectional association with severe fatigue (23, 25, 60, 64, 65). Routine screening for anxiety and depressive symptoms should take place in the management of fatigue.

Behavioural factors

Patients with sarcoidosis have various coping mechanisms for their disease, and these can play a role in fatigue. Patients who find it difficult to cope are more likely to have disabling symptoms (23, 42). With this in mind, some patients might benefit from cognitive behavioural therapy (CBT) to help improve coping and management skills (25). Moreover, general behavioural factors such as excessive alcohol and caffeine intake, low social support, and inactivity can also play a role in the persistence of fatigue, and should be assessed regularly and managed if present.

Treatment of fatigue

Once secondary causes of fatigue are excluded, there are several non-pharmacological and pharmacological interventions proposed as treatment for sarcoidosis-associated fatigue. Physical activity programmes including physiotherapy and pulmonary rehabilitation were found to be effective in reducing fatigue in sarcoidosis (66–68). Therapy-based treatments, such as mindfulness training and CBT, seemed to have a positive effect on fatigue in two small studies. These non-pharmacological treatment options are discussed in more detail at the end of this chapter.

Table 1 Patient-reported outcome measures often used to evaluate non-organ manifestations of sarcoidosis

	Development and main characteristics	Short description	Cut-off values/MCID
Global assessment of symptoms			
Visual analogue scales (28, 29)	• Not validated in sarcoidosis • Validated in other chronic disorders (also in interstitial pulmonary fibrosis)	• Psychometric response scale: left side of the line represents lowest scores (lesser symptoms), the right side of the line highest score (worse symptoms)	
Fatigue			
SAT-fatigue (30)	• Developed to assess manifestations of sarcoidosis • Eight domains, including fatigue	• Five items on fatigue, answered on a 5-point Likert scale • Maximum score 25	• Estimated MCID 3.1 • Validation of cut-off values: work in progress
Fatigue assessment scale (31, 32)	• Developed to measure fatigue in patients with sarcoidosis	• Self-report questionnaire, 10 question (five on physical fatigue and five on mental fatigue) answered on a 5-point Likert scale • Maximum score 50	• Fatigue: score ≥22 • Extreme fatigue: score ≥35 • MCID 4
OSA			
Epworth Sleepiness Scale (33,34)	• Originally developed to assess daytime sleepiness • Also used as a tool for comprehensive assessment of OSA	• Self-report questionnaire, - Eight questions answered on a 3-point Likert scale • Maximum score 24	• Score >10 signifies daytime sleepiness
STOP-BANG Questionnaire (35,36)	• Originally developed to assess the risk of OSA in pre-operative patients	• Four dichotomous questions on OSA-related symptoms and four clinical characteristics • Maximum score 8	• Score 0-2: low risk of OSA • Score 3-4: intermediate risk of OSA • Score 5-8: high risk of OSA
Pain			
Numeric pain rating scale (37,38)	• Developed to measure pain intensity in adults • High reliability and validity in patients with rheumatic pain	• Unidimensional measurement of pain • 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable)	• Higher scores indicate greater pain intensity
SAT-pain interference (30)	• Developed to measure manifestations of sarcoidosis • “Pain interference” one of eight modules	• Pain module consist of five questions answered on a 5-point Likert scale • Maximum score 25	• Estimated MCID 3.2 • Validation of cut-off values: work in progress
Small Fiber Neuropathy			

TABLE 1 Continued

	Development and main characteristics	Short description	Cut-off values/MCID
Small Fiber Neuropathy Screening List (39,40)	• Developed to assess SFN in patients with sarcoidosis • Two parts: experience of specific complaints and severity of complaints	• Self-report questionnaire • 21 questions answered on a 5-point Likert scale • -Score range from 0-84	• Score <11: few or no SFN-related symptoms • Score 11-48: probable or highly likely SFN • Score >48; indicative of SFN • MCID 3.5
Depression/anxiety			
Abbreviated Centers for Epidemiologic Studies-Depression Scale (6, 41)	Developed to assess the presence and severity of depressive symptoms; has high validity and reliability	• 11-item self-reporting tool modified from the original 20-item self-reporting tool • Questions are answered on a 3-point Likert scale • Score range 0-33	• Score >9 indicates depression
Hospital Anxiety and Depression Scale (7, 8, 11, 42, 43)	Developed to assess anxiety and depression among non-psychiatric patients	• 14-item self-reporting tool in the domains of anxiety and depression • Questions are answered on a 3-point Likert scale • Score range for separate domains 0-21	• Score 0-7: no anxiety or depression • Score 8-10: possible anxiety or depression • Score 11-21: probably anxiety or depression
Anxiety Sensitivity Index-3 (7, 42, 44)	Designed to assess for anxiety sensitivity in the domains: physical concerns, cognitive concerns, and social concerns	• 18-item self-reporting tool • Questions are answered on a 5-point Likert scale • Score range 0-90	Higher scores signify more anxiety
Cognitive impairment			
Cognitive Failure Questionnaire (12, 13)	Developed to asses impairments in perception, memory, and motor function	• 25-question assessment tool • Questions are answered on a 5-point Likert scale • Score range 0-100	Higher scores signify more cognitive failure

Specific quality-of-life measurement strategies and results of studies from sarcoidosis-specific patient-reported outcome measures are reviewed in detail in chapter 23 (19).
MCID: minimal clinically important difference;

SAT: Sarcoidosis Assessment Tool; OSA: obstructive sleep apnoea; STOP-BANG: snoring, tiredness, observed apnoea, high blood pressure, body mass index, age, neck circumference and male gender questionnaire; SFN: small-fibre neuropathy.

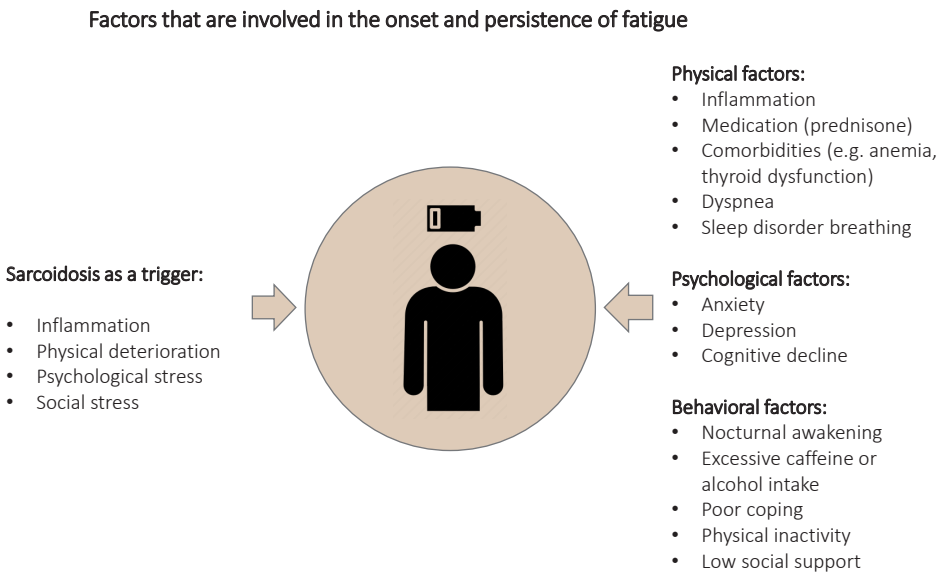


Figure 3. The various factors that play a role in the onset and persistence of fatigue in sarcoidosis

Two small randomised controlled trials (RCTs) investigated the effect of neurostimulants on fatigue (methylphenidate and armodafinil) (69, 70). The European Respiratory Society (ERS) guidelines suggest neurostimulants in cases of exercise-based treatment strategy failure (71). Neurostimulants increase dopamine and noradrenaline within the brain and could potentially have a positive effect on fatigue. Several contraindications must be considered before prescribing these agents: among others, the presence of cardiovascular disease, cerebrovascular disease and a history of psychotic symptoms or severe depression. While the results of these studies are promising, more research on the efficacy of neurostimulants is needed. A larger RCT for methylphenidate has been deemed feasible (72).

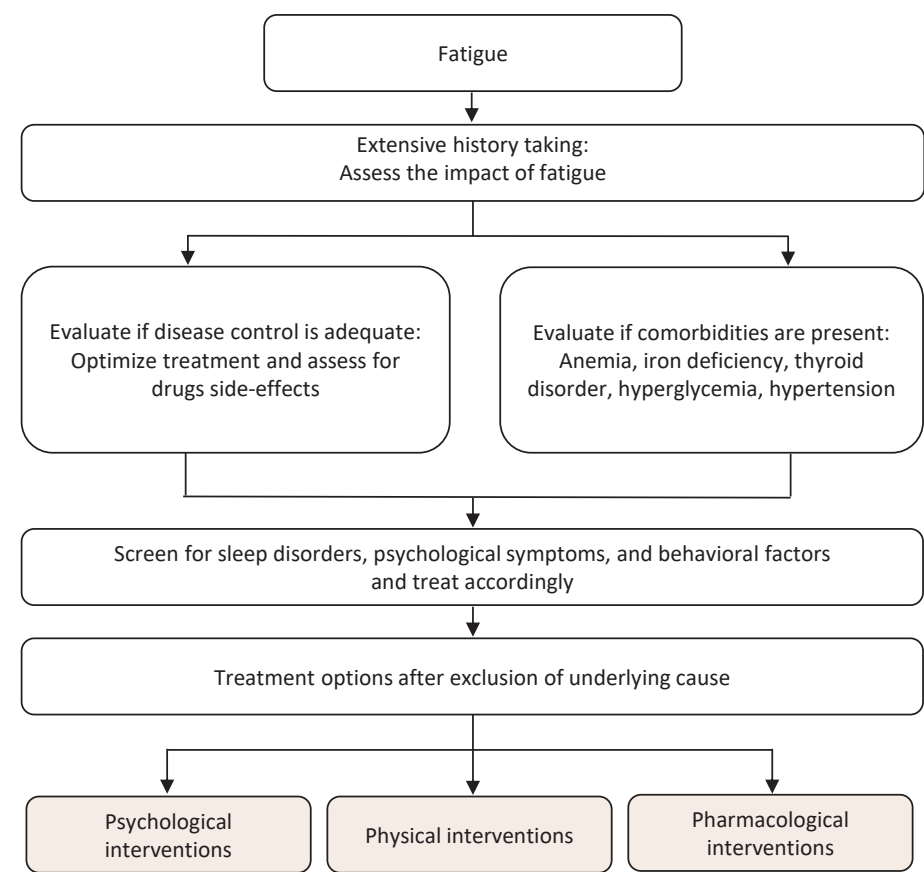


Figure 4. Algorithm for the assessment and management of fatigue in sarcoidosis patients.

The discrepant impact of corticosteroids on fatigue may be due in part to the presence or absence of inflammation during use. Some studies showed that corticosteroids use seem to have a negative impact on fatigue (49, 50). Controversially, dexamethasone 1 mg daily has been shown to improve fatigue based on PROMs from 3 months to 12 months of follow-up (73). Notably, in the BTS guidelines, a non-unanimous consensus was reached to treat fatigue with steroids (no consensus dosage), but the authors did acknowledge that only a minority of patients with fatigue would improve with this strategy (74). Several studies have suggested a positive effect of anti-TNF- α treatment on fatigue, but this was only assessed as a secondary end-point (75, 76).

Pain

Pain is a frequent symptom in individuals with sarcoidosis and is associated with high morbidity related to impact on HRQoL, sleep and functional status (77). This symptom can manifest in multiple ways, including headaches, chest pain, abdominal pain, back pain, musculoskeletal complaints and SFN (5, 14, 77–81). Sarcoidosis providers should assess for pain regularly and treat accordingly, although chronic pain can be difficult to manage, as anecdotally it is often refractory to opioid and non-opioid analgesics (82). A primary reason for treatment challenge lies in the fact that pain may be secondary to disparate causes including sarcoidosis granulomatous aetiologies (e.g. chest pain due to thoracic lymphadenopathy, skeletal pain due to bone involvement), sarcoidosis non-granulomatous aetiologies (e.g. chest pain due to chronic cough, SFN) and a broad range of non-sarcoidosis aetiologies (e.g. migraine, spinal pathology) (77, 79, 83, 84). To optimise treatment decisions, clinicians need to examine for and differentiate between the various aetiologies of pain. Note that pain related to granulomatous inflammation including chronic arthralgias/myalgias, as well as SFN, are discussed in detail elsewhere in this Monograph (18).

Chest pain

Chest pain in sarcoidosis is frequently substernal and/or intrascapular (4, 5). In a single-centre study, chest pain occurred in 64% of individuals with sarcoidosis, and was the most burdensome symptom in close to a third of cases (4, 5). However, the true prevalence of chest pain in sarcoidosis is unknown, since it has never been studied systematically in large clinical trials and no registry studies have published such data. As chest pain can also be driven by non-sarcoidosis organic aetiologies including angina, pericarditis, pulmonary embolism, gastro-oesophageal reflux and other oesophageal pathology, a thorough history and evaluation should be performed to exclude these aetiologies. Sarcoidosis-related chest pain is likely to be multifactorial; early studies suggested that pain is related to granulomatous inflammation with resultant anatomic distortion of intrathoracic lymph nodes, breasts, chest wall or the oesophagus, which may be radiographically apparent in a minority of patients (5). In contrast, one prospective study suggests that this pain is independent of anatomic abnormalities and may be secondary to chronic cough based on the lack of associated CT abnormalities and pleuritic nature in the majority of cases (4). In a cohort of patients with sarcoidosis presenting with typical and atypical anginal chest pain, symptoms were suspected to be due to microvascular vasospasms triggered by myocardial sarcoidosis, as suggested by abnormal thallium myocardial scintigraphy and normal coronary angiography in the majority of patients (84).

Headaches

Headaches appear to be common in sarcoidosis. A single-centre cohort study reported migraine affecting nearly 30% of 96 patients with sarcoidosis, versus 13% of healthy controls (14). Notably, the presence of neurosarcoidosis or immunosuppression was not significantly associated with migraine development, suggesting that this symptom may be independent of granulomatous inflammation (14). These results should be interpreted with caution, as the study sample size was small and it remains uncertain if there is truly a greater risk of headaches in patients with sarcoidosis.

Assessment of pain

There is no standardised sarcoidosis-specific metric with a primary emphasis on pain, though the SAT “pain interference” module has a moderate correlation with other validated pain scales and is a potential tool for future studies evaluating pain in sarcoidosis (30). Pain related to SFN can be assessed using the Small Fiber Neuropathy Screening List (39, 40). Additionally, the numeric pain rating scale or visual analogue scale (VAS) can be rapidly employed to assess pain (Table 1).

Pain management

The first step in pain management is a thorough assessment to identify whether pain is of a sarcoidosis or a non-sarcoidosis organic aetiology. Dependent on the site of pain, a multidisciplinary approach is useful to guide and narrow this assessment. There are no data-driven guidelines regarding pain management, and treatment is based on underlying aetiology. Pain attributed to granulomatous inflammation may respond to corticosteroids, although there are data to suggest that this response can be limited (49). Anti-TNF- α therapies such as infliximab and intravenous immunoglobulin have been studied in SFN (85–87). However, the recent ERS clinical practice guideline did not provide a recommendation on these therapies due to the lack of evidence (71). Additionally, pain attributed to sarcoidosis non-granulomatous changes may respond to over-the-counter and topical analgesics such as non-steroidal anti-inflammatories, acetaminophen, lidocaine cream/gel and capsaicin patches. Anticonvulsants such as gabapentin, pregabalin and topiramate, as well as tricyclic antidepressants are also frequently used in the management of sarcoid SFN, but strong evidence to support this practice is lacking (88). Finally, in an early-phase safety study, ARA-290 (cibinetide), a small peptide activating anti-inflammatory and tissue repair pathways, has been shown to reduce pain and neuropathic symptoms in patients with sarcoidosis (89, 90).

Psychological stress and cognitive dysfunction

Sarcoidosis is associated with a high burden of depression, anxiety, memory impairment and poor concentration (6–8, 11, 12, 91). There is a complex interplay between these psychological and cognitive impairments with fatigue, HRQoL and additional organ-specific and non-organ manifestations of disease including dyspnoea, skin changes and pain (20, 42, 44, 64, 92–96).

Depression and anxiety

Assessment of depression and anxiety

While true prevalence is challenging to define, depression is estimated to occur in 30–60% of patients with sarcoidosis; this is substantially greater than the general population, and slightly higher than in individuals with other chronic interstitial lung diseases (ILDs) (6–8, 97, 98). Given the high estimated prevalence, screening for depression could be considered in all sarcoidosis patients, and special attention should be given to those with risk factors for depression including female sex and those with poor access to care, multiorgan involvement and the presence of dyspnoea and other comorbidities (6, 8). While there are no sarcoidosis-specific metrics that screen for depression in isolation, the Sarcoidosis Health Questionnaire is designed to assess HRQoL including emotional wellbeing (99). An abbreviated Centers for Epidemiologic Studies Depression Scale was used to identify depression in a heterogeneous population of sarcoidosis patients in the United States (6, 100). The Hospital Anxiety and Depression Scale (HADS) is another well-validated self-report tool that has been used to identify anxiety and depression in sarcoidosis (**Table 1**) (7, 8).

Anxiety presents as frequently as depression, with an estimated prevalence of 30–50% (7, 8, 11). Anxiety sensitivity, or fear of anxiety-provoking symptoms, is a related but distinct entity that is also common in sarcoidosis and can be evaluated with the Anxiety Sensitivity Index-3 (**Table 1**) (7, 44, 101). As noted previously, there is an interdependent relationship between anxiety, anxiety sensitivity and other psychological and non-psychological manifestations of sarcoidosis. Specifically, high levels of anxiety and anxiety sensitivity are strongly associated with clinical symptoms, and, conversely, fatigue and clinical symptoms, including dyspnoea, predict anxiety (7, 8, 42). Strikingly, anxiety sensitivity was found to be a stronger predictor for dyspnoea severity in sarcoidosis than other traditional metrics, including FVC (44). With these details in mind, it is important to evaluate for and treat anxiety and anxiety sensitivity in all patients, even when primarily presenting with physical, organ-specific symptoms.

Management of depression and anxiety

Studies have failed to show a clear improvement in depressive symptoms following treatment with corticosteroids, and in fact their use may lead to worsening psychiatric symptoms, as mood swings and depression are well-known side effects of these medications (50, 73, 96). Treatment with corticosteroids should be re-evaluated when depressive symptoms are present, and use of immunosuppressive medications for treatment of depression in isolation should be avoided. There are no studies to date evaluating depression as a primary outcome of any specific intervention in patients with sarcoidosis. Reduced depressive symptoms was a secondary outcome noted in a multicentre study evaluating a 3-week inpatient pulmonary rehabilitation programme for patients with sarcoidosis. Since the study was not powered to detect improvement in depression specifically, these results warrant further study (102). With all this in mind, for patients with sarcoidosis with depression, the current approach is to offer traditional management strategies including counselling and psychotherapy with or without antidepressants and anxiolytics.

Treatment of anxiety with mind–body medical techniques including meditation, yoga, tai chi and biofeedback could be considered along with more traditional treatments for anxiety including counselling, antidepressants and anxiolytics (88).

Cognitive impairment

Assessment of cognitive impairment

Cognitive impairments, specifically memory difficulties and poor concentration, are estimated to occur in one-third of general sarcoidosis patients and 50% of the neurosarcoidosis population (12, 13). Cognitive failure in sarcoidosis may be measured by the Cognitive Failures Questionnaire (CFQ) (**Table 1**) (12, 20, 103). Given the associations between cognitive failure, fatigue, symptoms of SFN and depression, it is useful to assess and manage psychological and non-psychological contributors to cognitive failure. Furthermore, patients should be screened for neurosarcoidosis when cognitive failure is present (12, 20).

Treatment of cognitive impairment

Regarding specific therapy, the use of corticosteroids and methotrexate (MTX) have not been shown to be clearly beneficial, although there is one small study suggesting that anti-TNF- α medications including infliximab and adalimumab are associated with decreased cognitive failure following 6 months of treatment, as measured by the CFQ (12). It should be noted that this was not a RCT and the control group included normal healthy patients from a separate study on ageing.

Multidisciplinary and overarching approach for management

Non-organ-specific manifestations significantly impair HRQoL in patients with sarcoidosis (**Figure 5**). One study showed that reduced HRQoL in sarcoidosis patients compared to the general population was particularly related to fatigue (104). Compared to the general population, patients with sarcoidosis experience a reduction in work ability as measured by earnings and lost work days for up to 5 years after diagnosis (105). Indeed, fatigue has been shown to be the single most important predictor of HRQoL in patients with sarcoidosis (106). Many patients express feelings of disregard from healthcare providers regarding symptoms of fatigue and pain (107). All these factors underline the burden that non-organ related manifestations place on patients as well as the healthcare system and the urgent need for adequate management strategies.

Multidisciplinary approach to management

An overall strategy to assess and manage these conditions starts with asking the patient simple questions to elicit whether fatigue, pain, depression, anxiety and cognitive impairment are present. Ideally, to structurally assess these symptoms, PROMs are used, but we acknowledge that these are not always feasible in a busy daily practice and there is a need for quick screening tools. VAS enable quick assessment and evaluation of symptoms. VAS have not been studied in sarcoidosis, but have been validated in other chronic diseases, including ILDs (29, 108).

Several studies have shown that anti-granuloma therapy targeting specific organ involvement does not necessarily improve HRQoL (60, 96, 109). A multidisciplinary approach that includes non-pharmacological and pharmacological interventions is needed (**Figure 6**). Physical activity-based modalities such as pulmonary rehabilitation programmes have been shown to impact HRQoL (110, 111). In one study of patients with pulmonary sarcoidosis, a 12-week pulmonary rehabilitation training programme which met for 90 min twice a week led to an overall improvement in perceived wellbeing and HRQoL as measured using the St George's Respiratory Questionnaire (SGRQ), which was durable for 3 months post-training (111). Along with HRQoL, several studies also show improvement in fatigue as measured by the FAS when a 12- or 13-week supervised physical training programme is provided (67, 68). An individualised, multimodal combination of treatments including pulmonary rehabilitation is recommended for sarcoidosis-associated fatigue in the BTS clinical statement on pulmonary sarcoidosis and in the ERS guidelines (71, 74).

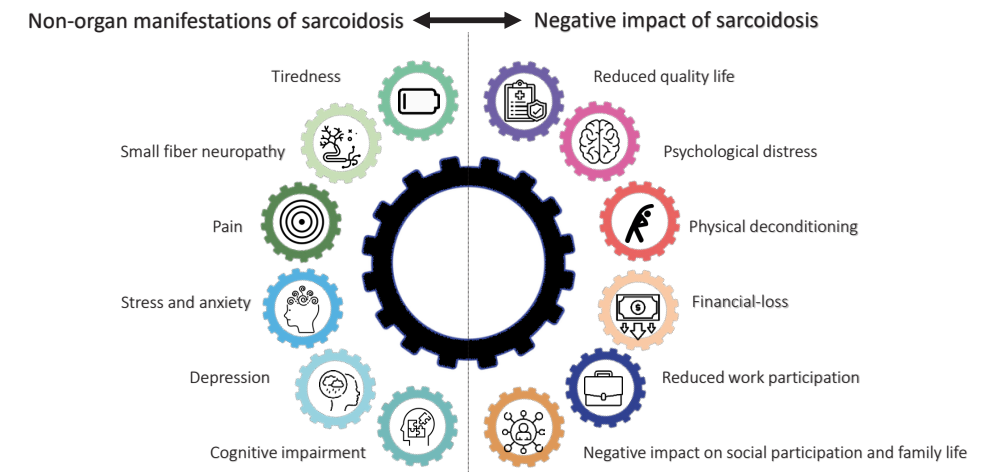


Figure 5 Non-organ manifestations of sarcoidosis and the impact on quality of life, as reported in the medical literature.

Several studies have evaluated the impact of pulmonary rehabilitation programmes on anxiety and depression using the HADS questionnaire, but the results have been mixed (111). One study of pulmonary sarcoidosis patients with Scadding stage 3 and 4 disease who received 12 weeks of structured and supervised exercise training showed improvement in anxiety (110). Another study with 300 patients using only a 3-week duration of pulmonary rehabilitation showed improvements in the HADS score, SGRQ score and FAS, suggesting that anxiety, depression and fatigue decreased (102). A RCT on the effect of an online 12-week tele-rehabilitation in sarcoidosis is ongoing (NCT03914027).

The effect of psychotherapy or counselling in patients with sarcoidosis has not been studied systematically. However, it is likely that these treatment modalities improve HRQoL and it is plausible that these therapies impact outcomes, since depression and anxiety are associated with worse clinical outcomes (95). Mindfulness training was studied in a small cohort of sarcoidosis patients, and showed decreased physical and psychological symptom burden (112). CBT has been shown to improve fatigue after 1 year of practice in a small pilot study (113). CBT has a positive effect on fatigue in other chronic diseases, and an ongoing RCT is investigating the efficacy of online CBT (Netherlands Trial Register number NL7816) (114). Related treatment strategies including tai chi have been shown to be effective in other chronic conditions, and may also be beneficial in patients with sarcoidosis (115). Counselling and psychotherapy can be employed concomitantly or alone, depending on the specific issues a patient is facing. If none of these strategies are effective, pharmacological therapies could be added, as alluded to earlier in this chapter.

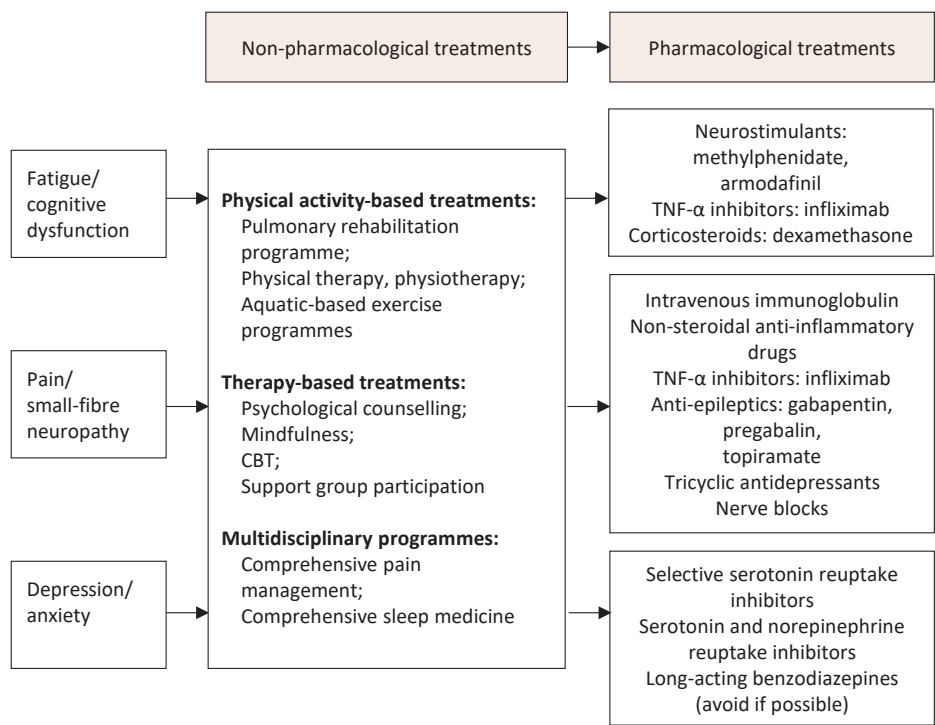


Figure 6. Non-pharmacological and pharmacological treatment options for non-organ-specific manifestations of sarcoidosis. If non-pharmacological treatments are unsuccessful, consider pharmacological treatments. In cases of disease activity, immunosuppressive therapy might be preferred before or simultaneously with non-pharmacological treatments. Please note that most of these pharmacological treatments are only studied in small cohort studies and evidence of efficacy is limited, therefore no recommendation could be made for these therapies in the recent European Respiratory Society clinical practice guideline. A careful consideration must be made before prescribing these agents. CBT: cognitive behavioural therapy.

Referrals to patient associations such as the Foundation for Sarcoidosis Research and Sarcoidosis UK can be helpful. These organisations provide education, access to support groups, nurse helplines and seminars incorporating physical activity, mindfulness, journalling and various other educational opportunities.

Socioeconomic status and other social determinants

When discussing HRQoL and non-organ related manifestations, we should keep in mind that socioeconomic status, implicit racism in the medical system and social determinants of care are intertwined with sarcoidosis and its outcomes (116). Harper et al. (117) showed that low-income sarcoidosis patients had worse HRQoL and outcomes. The landmark study, A Case-Control Etiologic Study of Sarcoidosis, was the first to demonstrate that low-income patients were more likely to be black and female and to encounter barriers to getting care (118). Access to multidisciplinary care may be even more limited for those with a low income, and the non-insured and under-insured. As a sarcoidosis community we need to be aware of these mechanisms and invest in ways to ensure equal access to care for all patients.

Future directions

Many physicians are unaware of non-organ-specific manifestations of sarcoidosis, so additional education and dissemination of these complications is imperative. Clinical trials for new therapies should also include fatigue and pain as end-points and research into the pathogenesis and management of fatigue, depression and pain should be encouraged. Studies that evaluate direct aetiology and those that investigate the interdependence with behavioural characteristics and clinical phenotypes are needed. In addition, objective tests/measures to determine the presence and severity of these manifestations is important. Collaborating with investigators in other areas such as neuroscience, muscle physiology and other conditions such as fibromyalgia and chronic fatigue syndromes could help advance the field. Finally, in order to make progress in our understanding and management of these manifestations, patient participation in the design of clinical trials of therapy and other studies is imperative.

Conclusion

Non-organ manifestations of sarcoidosis are common, but under-recognised. Management of these conditions is complicated by the lack of good insights in the pathogenesis and the multifactorial interactions. More research in this field is needed, as these conditions have a significant impact on quality of life, but are challenging to diagnose and treat. PROMs can help to screen for these conditions. Treatment should start with non-pharmacological measures since limited data are available to support pharmacological efficacy. Physical activity-based treatments can help improve fatigue, anxiety and depression. Other modalities such as psychological counselling and support groups can help. The impact of race and socioeconomics on patients with sarcoidosis and their outcomes should be considered. Patient participation in clinical trials and research in these conditions could help us gain greater understanding of the conditions.

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Chapter 9

Managing fatigue in patients
with interstitial lung disease



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Vivienne Kahlmann, MD; Catharina. C. Moor, MD;
and Marlies. S. Wijsenbeek, MD, PhD

Department of Respiratory Medicine, Erasmus Medical Center,
Rotterdam, The Netherlands

Abstract

Fatigue is one of the most burdensome symptoms in interstitial lung disease (ILD) and can have a major impact on quality of life, social interactions, and work capacity. The cause of fatigue is complex; it is caused or aggravated by a combination of different predisposing, precipitating, and perpetuating factors. There is no uniform definition of fatigue, but it is often divided into physical and mental components. Several validated questionnaires can be used for structural assessment of fatigue in daily care. Although the high burden of fatigue in ILD is increasingly recognized, studies that have investigated pharmacologic and nonpharmacologic treatment options are scarce. Because fatigue in ILD is often a multifactorial problem, therapeutic interventions ideally should be aimed at different domains. One of the first steps is to optimize treatment of the underlying disease. Subsequently, treatable causes of fatigue should be identified and treated. Recently, an increasing number of studies showed that supportive measures have the potential to improve fatigue. However, evidence-based treatment guidelines are lacking, and more research is highly needed in this field. In clinical practice, a comprehensive, multidisciplinary, and individually tailored approach seems best fit to optimize treatment of fatigue in patients with ILD.

Introduction

Interstitial lung disease (ILD) is a broad term for a group of >200 rare lung diseases. Some of these diseases are mainly inflammatory, while others are more fibrotic from the start, and many are a combination of both. This diversity in underlying pathobiologic conditions is also reflected in the variable clinical disease behaviour: some ILDs are reversible; some have the potential to stabilize, and some have a progressive fatal course (1). ILDs often have a major impact on patients' quality of life (QoL), daily living, work capacity, and social interactions (2). Most frequently reported symptoms are cough, dyspnea, and fatigue (3-5). Although the impact of fatigue is widely acknowledged, there is limited information about the cause and management of fatigue in ILDs. Most studies are conducted in patients with sarcoidosis, and, more recently, some small studies have been published on other ILDs. In this review, we will give an overview of the most recent insights of fatigue in ILD.

Case Report

A 37-year-old man presented at our outpatient clinic with sarcoidosis. His most burdensome symptoms were a dry cough and fatigue. The radiograph showed bilateral lymphadenopathy and discrete nodular abnormalities in the upper lobes. Pulmonary function tests were normal. Blood testing showed normal blood count and liver and kidney test results. Calcium and thyroid-stimulating hormone levels were also normal, while the soluble IL-2 receptor (sIL-2R) level was slightly elevated. Additional examination revealed OSA, for which he was treated successfully with CPAP, which resulted in his apnea-hypopnea index becoming normalized. However, fatigue did not improve. On follow-up, his radiograph spontaneously improved; pulmonary function test results remained normal, and his sIL-2R normalized.

Consultation with the cardiologist revealed no abnormalities. Subsequently, treatment with methylphenidate was initiated without success. Considering the major negative impact of fatigue on his QoL, we referred him to a psychologist for cognitive behavioural therapy.

Prevalence of fatigue in ILD

In the general population, fatigue is reported in 5% to 20% (6). Although fatigue is often reported as a common symptom in ILD, data on prevalence in different ILDs are scarce (**Figure 1**). In idiopathic pulmonary fibrosis (IPF), fatigue is reported in up to 95% of patients (4,7). In the European IPF registry, prevalence of fatigue was similar for patients with IPF (69.2%), compared with patients with non-IPF ILDs (70.6%). In systemic sclerosis studies, fatigue was present in up to 89% of the patients (8). In chronic hypersensitivity pneumonitis, fatigue has been reported in up to 87% of patients (9). A recent multinational survey showed that fatigue was present in 90% of patients with sarcoidosis, with up to 48% of patients mentioning extreme fatigue (5). Fatigue mostly occurs at disease onset and during the active phase of sarcoidosis. Nevertheless, even up to 56% of the patients with complete remission report fatigue (10). The prevalence of fatigue in different ILDs is difficult to compare, because different questionnaires were used. It also depends on whether fatigue is patient- or physician-reported. For instance, in a sarcoidosis registry study, physicians only reported fatigue in 30% of the patients, which is much lower than patient-reported fatigue in other studies (5,11). This emphasizes the importance of regularly asking patients whether fatigue is present.

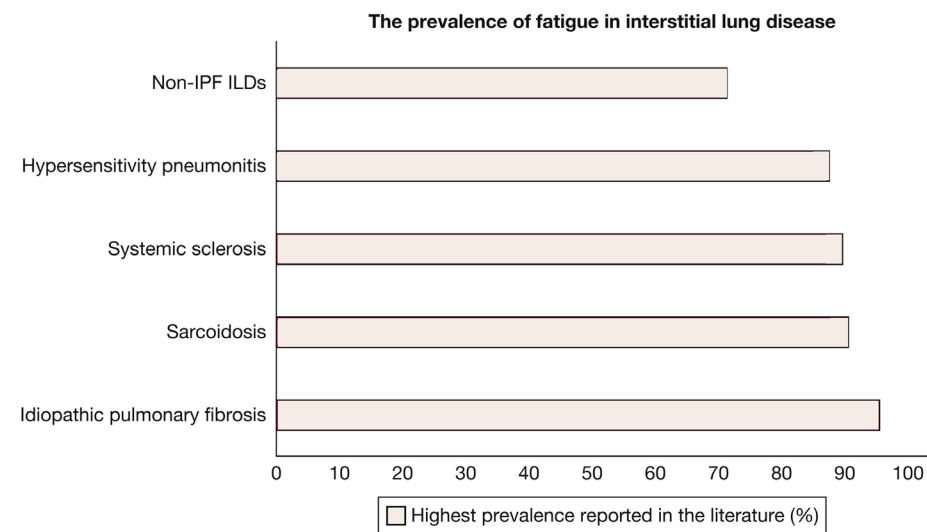


Figure 1. Reported prevalence of fatigue in interstitial lung disease. ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis.

Cause of Fatigue in ILD

One of the complicating factors in studying fatigue is that there is no uniform definition of fatigue, although it is often divided into a physical and a mental component (6,12). Mental fatigue (perceived fatigability) can be described as a subjective symptom of malaise, tiredness, lack of energy, and aversion to activity (6,12,13). Physical fatigue (performance fatigability) refers to impaired physical performance (6,12). The cause of fatigue is poorly understood; however, physiologic, psychologic, and behavioural factors seem to play a role in the onset and persistence of fatigue (6,13). In most sarcoidosis studies, fatigue is poorly correlated with clinical parameters. However, in IPF and systemic sclerosis, there seems to be an association with disease severity (7,14-16). Many uncertainties still exist about the cause of fatigue, which are likely not ILD-specific.

Fatigue is a prevalent symptom in many chronic disorders (17). A 2018 study demonstrated that only 11% of the variation in fatigue could be explained by the specific diagnosis. In this study, fatigue was explained mainly by transdiagnostic factors, such as reduced motivation, pain, limitations in physical functioning, concentration problems, reduced activity levels, poor sleep quality, and the ability to cope with fatigue (17).

From other areas outside ILD, we have learned that factors that influence fatigue can be divided into predisposing factors, precipitating factors, and perpetuating factors (6,13). For a large part, many of these factors also hold true for ILD (Fig 2). Patients with predisposing factors such as biologic vulnerability, vulnerable personality, and lack of support are at increased risk of experiencing fatigue (6,18). In different forms of ILD, physical deterioration, psychological stress, and social stress have been described as precipitating factors that can cause fatigue (2,7,8,16). Furthermore, there is a wide range of physical, psychological, and behavioural factors that may further perpetuate fatigue and are described in more detail later.

Perpetuating Factors

Physical and Psychological Factors:

Poor sleep quality is reported more frequently by patients with ILD than in the general population (16,19,20). Sleep architecture is often disrupted, with a decrease in rapid eye movement sleep, increase of sleep fragmentation, and more nocturnal desaturations compared with the general population (20,21). In a study on sleep quality in 15 patients with IPF, a significant correlation was

found between nocturnal saturation and fatigue scores (22). Whether nocturnal supplemental oxygen has an effect on sleep quality and fatigue has not yet been studied. Other ILD-related factors that may alter the sleep architecture are cough, periodic limb movement, restless legs syndrome, and the side effects of medication such as corticosteroids (19,20). Another reason for fatigue may be OSA, with a reported prevalence of up to 88% in ILD (20,21). The high prevalence of OSA could be explained partly by comorbidities, such as obesity or upper airway pathologic conditions. However, one study showed that, even when these comorbidities were excluded, OSA was found in 68% of the patients with ILD (82.3% in IPF, 66.6% in sarcoidosis, and 55.5% in systemic sclerosis). Another explanation proposed for the high prevalence of OSA is the upper airway collapse caused by the restrictive lung disease (20).

It has been suggested that low-grade inflammation may play a role in fatigue; however, not many data for this exist in ILD. A study in patients with sarcoidosis who were in clinical remission demonstrated that a decrease in Th2 cytokine production was associated with fatigue (23). However, most studies have not found a relation between serologic markers (such as angiotensin-converting enzyme), sIL-2R and C-reactive protein, and fatigue (24). Furthermore, fatigue often persists in patients with sarcoidosis who are in clinical remission and have no signs of active inflammatory response (10).

Medication is another factor that may cause or aggravate fatigue. Different studies have shown that corticosteroids are associated with fatigue and impaired QoL in sarcoidosis (25). Because fatigue is a registered common side-effect of corticosteroids, this may also play a role in other ILDs. Overall, corticosteroids often lead to side effects such as weight gain, sleep disturbance, psychological disturbance, and diabetes mellitus, which are also associated independently with fatigue (20,24). Current treatment of IPF consists of the antifibrotic drugs nintedanib and pirfenidone (26). Fatigue is one of the registered side effects of pirfenidone (26). Pooled data of the pirfenidone trials showed that fatigue occurred as an adverse event in 26% of the pirfenidone group and 19% of the placebo group (27). In an observational study on the long-term safety of pirfenidone in IPF, fatigue was reported as one of the most common adverse drug reactions in 18.5% of patients (28).

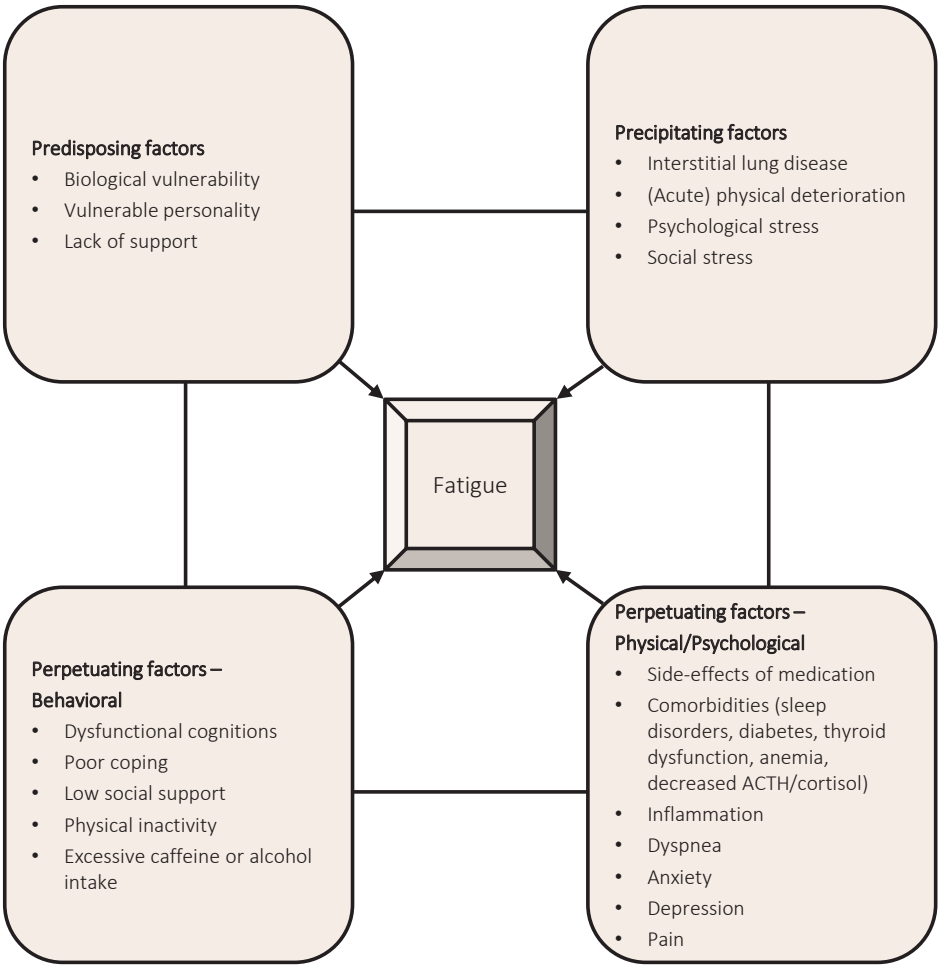


Figure 2. Predisposing, precipitating and perpetuating factors that can cause or aggravate fatigue in interstitial lung disease. Most of these factors are interrelated, and some are related in a bidirectional way. ACTH = adrenocorticotrophic hormone.

Other comorbidities that are associated with fatigue are diabetes mellitus, thyroid dysfunction, anemia, iron deficiency, and decreased adrenocorticotrophic hormone/ cortisol levels (2,24,29). Evaluation of the presence of these comorbidities is important, because many are found to be more prevalent in ILDs and may impact not only fatigue but also influence the disease course. For instance, in patients with IPF, hypothyroidism and diabetes mellitus are more prevalent and are also associated with worse prognosis (16,29-31).

Some small observational studies have found an association between physical activity, which was measured with wrist-worn activity trackers, and fatigue in patients with ILD (10,32,33). Patients who were less active seemed to be more tired. The association between activity and fatigue seemed stronger in patients with IPF than in patients with sarcoidosis (32,33). Most patients with IPF report fatigue as physical exhaustion, while patients with sarcoidosis mainly report mental fatigue (7). This may explain the reason that fatigue is correlated more strongly with physical activity in IPF than in sarcoidosis. Other physical factors associated with fatigue in ILD are dyspnea, muscle strength, and pain (10,13,15).

Anxiety, depressive symptoms, memory loss, and concentration problems (cognitive failure) are related to fatigue in a bidirectional way (34). Psychological symptoms are more prevalent not only in ILDs but also in other chronic diseases (7,8,16,17). Uncertainty about prognosis and a decrease in social and work participation are some of the factors that lead to increased stress and anxiety in ILD (2,35). In patients with (self-reported) cognitive impairment, normal daily tasks require more cognitive effort, which in turn might lead to higher fatigue levels (34). In sarcoidosis, small fiber neuropathy is reported frequently and is associated strongly with fatigue (5,34).

Behavioural Factors:

In general, behavioural factors, such as dysfunctional cognitions, poor coping, inactivity, excessive caffeine or alcohol intake, and low social support, can perpetuate fatigue (13). These factors have not been evaluated specifically in ILD in relation to fatigue. However, some of the aforementioned factors potentially could be managed by simple interventions and support from a social worker or psychologist.

Therefore, we believe that behavioural factors should not be overlooked in the assessment and treatment of fatigue in ILD.

The Impact of Fatigue

Fatigue has a huge impact on many aspects of the lives of patients that include social relationships, work participation, and QoL. Many patients consider fatigue to be a very burdensome symptom (5,16). The impact of fatigue may be difficult to understand for family, friends, employers, and health care professionals because it is a nonspecific symptom and patients often look completely healthy. Consequently, some patients feel that they are not taken seriously, which may lead to further social isolation (2,6,34). Fatigue has been reported to be an important negative predictor of QoL in patients with ILD and has been found to be associated with depression and anxiety, both in patients with sarcoidosis as well as with other ILDs (16,34).

Furthermore, fatigue is associated with decreased work participation, loss of income, and social isolation (36-38). In turn, a low income has also been associated with the development of sarcoidosis-related comorbidities, such as fatigue (39). In a study on work performance in sarcoidosis, 43% of 755 patients underwent disability evaluation. In these patients, fatigue levels were significantly higher than in the group who had not undergone work capacity assessments.

Measurement of Fatigue

Although highly prevalent, fatigue is often not structurally assessed in patients with ILD. Evaluating fatigue can be challenging due to the different determinants of fatigue and the lack of a uniform approach (12). Obviously, active evaluation of fatigue and other burdensome symptoms should take place during every visit. Extensive history taking is needed to assess the severity and impact of fatigue on patients' lives and to identify possible perpetuating factors. In addition to this, different questionnaires can be used for a more structured evaluation of fatigue. The Fatigue Assessment Scale (FAS) and the Sarcoidosis Assessment Tool fatigue subscale were developed to assess fatigue in patients with sarcoidosis. The FAS is used most commonly, also in other ILDs. It consists of ten questions on a five-point response scale; five questions about physical fatigue and five questions about mental fatigue. The total score ranges from 10 to 50 points; a score of ≥ 22 points indicates fatigue and ≥ 35 points severe fatigue. The minimal clinical importance difference is 4 points (40). The Sarcoidosis Assessment Tool fatigue subscale consist of five questions and is incorporated in a QoL questionnaire. Other questionnaires that have been used to measure fatigue in ILD are the Functional Assessment of chronic illness Therapy-Fatigue and the Patient-Reported Outcomes Measurement Information Systems Fatigue Instrument (41). These questionnaires may be used not only to quantify fatigue in clinical trials but also to assess the effect of treatment for individual patients in clinical practice.

Treatment of Fatigue in ILD

Even though the high burden of fatigue in ILD is well-recognized, studies that have investigated treatment options are limited. Because fatigue in ILD is often a multidimensional problem, therapeutic interventions ideally should be aimed at the different domains that are involved. **Figure 3** shows a decision-making flowchart on how to handle fatigue in ILD.

One of the first steps is to optimize treatment of the underlying disease and to exclude the possibility that fatigue is a side effect of prescribed medication. The side effects of corticosteroid use, especially, should be monitored thoroughly, and the prescribed dosage should be reassessed regularly and down-titrated if possible. Subsequently, treatable causes of fatigue should be excluded. As mentioned before, one of the treatable causes of fatigue in ILD is OSA. Two studies in IPF concluded that effective CPAP treatment improved daily living activities, quality of sleep, QoL, and daytime fatigue (21,42). Currently, a trial is ongoing to assess the prevalence and the effect of CPAP treatment in patients with sarcoidosis with OSA (43). Comorbidities, such as hypothyroidism, should be treated optimally, although no studies have reported on the effect of treatment of comorbidities on fatigue (30). In patients with depression, anxiety, or stress, referral to a psychologist could be considered. Because a high symptom burden of the underlying disease may also lead directly or indirectly to fatigue, treatment should also be directed at symptom relief. At the moment, a randomized controlled trial is assessing the effect of advancing symptom alleviation with palliative treatment in ILD. In that study, the intervention group is supported by a nurse and social worker with the aim of relieving burdensome symptoms, such as fatigue (44).

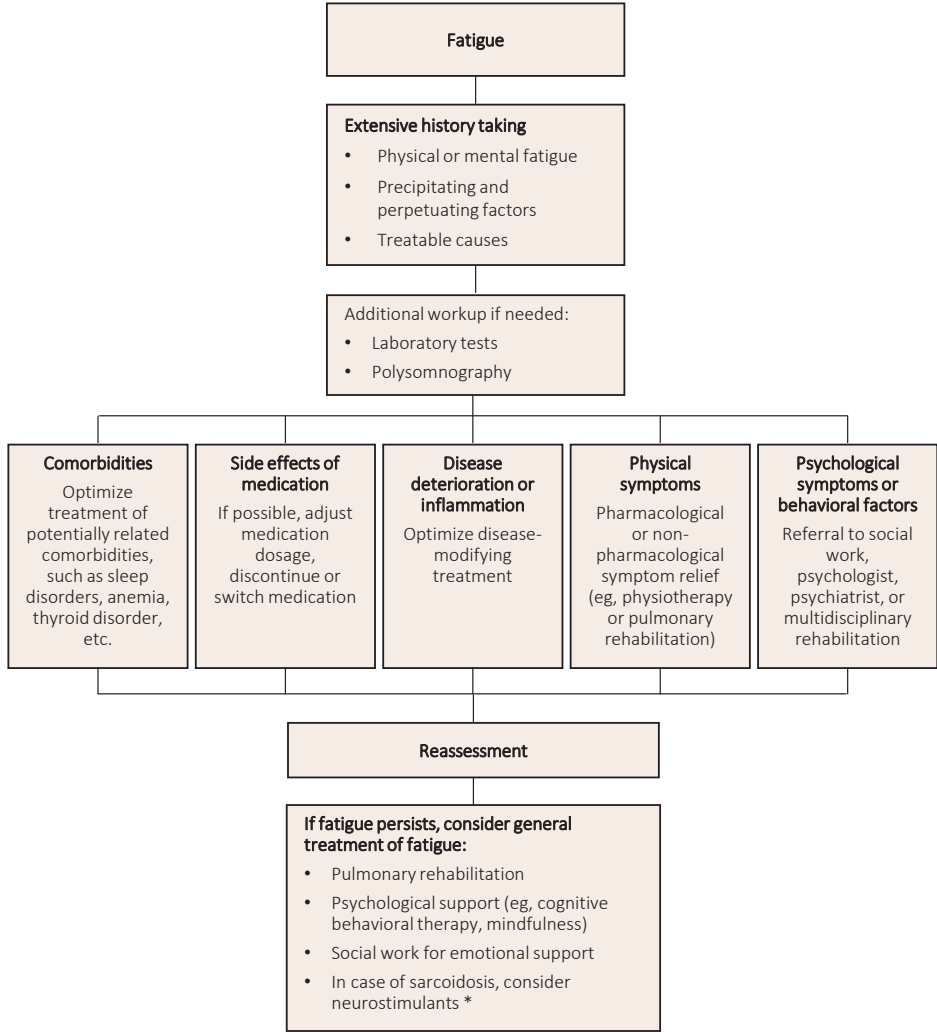


Figure 3. Decision-making flowchart on how to manage fatigue in interstitial lung disease. The asterisk indicates limited evidence, prescribe with caution.

When all systemic treatable causes have been excluded, the focus should be on the other domains. As far as possible, behavioural, precipitating, and perpetuating factors should be identified and, where possible, targeted. There is increasing evidence that exercise therapy or pulmonary rehabilitation could be beneficial in patients with ILD and fatigue. Pulmonary rehabilitation is a comprehensive intervention that consists of exercise training, education, and self-management strategies (45). One study showed a positive effect of a 6-week pulmonary rehabilitation program on fatigue in IPF (45). The treatment guideline of IPF also recommends pulmonary rehabilitation to alleviate symptoms (26). A randomized trial with patients with different ILDs demonstrated that an 8-week supervised exercise program improved fatigue scores, exercise capacity, and QoL (46). Similar positive results were found in sarcoidosis studies (47). Next to pulmonary rehabilitation, cognitive behavioural therapy has been proposed as a potential treatment option for patients with sarcoidosis-associated fatigue (2). A pilot study in sarcoidosis showed that a 45-minute mindfulness-based workshop improved fatigue and other symptom scores directly after the intervention (48). Long-term effects of this mindfulness workshop have not yet been evaluated. At the moment, a randomized controlled study to evaluate the effects of a 12-week online cognitive behavioural therapy in patients with sarcoidosis-associated fatigue (FAS score, ≥ 22 points) is ongoing (49). Although cognitive behavioural therapy has also been suggested in IPF, no studies have been conducted to date. Because fatigue is also perpetuated by inactivity, low social support, and psychological wellbeing, tailored interventions by physiotherapists, psychologists, or social workers may sometimes improve symptoms.

Neurostimulants have been suggested as potential treatment options for fatigue in sarcoidosis. The effect of dexamethylphenidate hydrochloride and armodafinil on sarcoidosis-associated fatigue was first described in 2008 (50,51). Dexamethylphenidate hydrochloride, which inhibits dopamine and noradrenaline in the brain, was studied in 10 patients. Armodafinil, which increases extracellular dopamine levels in the brain and is mainly used in narcolepsy, was studied in 15 patients. Both of these neurostimulants led to a significant improvement in fatigue scores and appeared to be safe. While the results of these studies were promising, only a small number of patients were included.

Currently, a new study on the effect and side effects of methylphenidate in sarcoidosis-associated fatigue is being conducted. This trial was mainly initiated to determine the feasibility and design of a future large-scale randomized, controlled trial. Hopefully, these results will enable larger scale future studies to provide better evidence for the use of neurostimulants for fatigue in sarcoidosis (52). The use of these agents has not been investigated, and their use cannot be recommended in other ILDs.

It has been suggested that anti-TNF- α treatment may have positive effects on sarcoidosis-associated fatigue; however, this finding has not been replicated in a randomized trial (53). At present, no studies have evaluated the effects of pharmacologic interventions in other ILDs.

Most of the data on how to deal with fatigue in ILD currently stem from sarcoidosis (41). Although we believe that there are many similarities between fatigue in chronic diseases and ILD and between sarcoidosis and other ILDs, important differences exist (2,7,16). Stable chronic diseases may have more general approaches; while in progressive fatal diseases like IPF, disease course and prognosis will also dictate treatment choices (54). In diseases with more rapid disease progression and worse prognosis, treatment of fatigue should be a part of integrated palliative care programs. To further advance insights into fatigue and develop better treatment strategies, more research obviously is needed. On one hand, the multifactorial cause in heterogeneous populations increases the complexity of the research; on the other hand, collaboration with partners outside the ILD research area could help to generate progress in the field, because fatigue is a universal problem in many chronic diseases.

Conclusion

Fatigue is a major problem both for patients with ILD and for treating physicians. The cause of fatigue in ILD is likely multifactorial, but many aspects are still unknown. Different predisposing, precipitating, and perpetuating factors contribute to fatigue, of which many also play a role in other chronic diseases. Unfortunately, specific guidelines and evidence-based treatment recommendations for fatigue are still lacking. In clinical practice, a comprehensive, multidisciplinary, and individually tailored approach seems to be the best fit to optimize treatment of fatigue in ILDs. Hopefully, new studies will lead to better treatment options for fatigue and ultimately improve QoL for patients with ILD.

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Chapter 10

Online mindfulness-based cognitive therapy for fatigue in patients with sarcoidosis (TIRED): a randomized controlled trial

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Vivienne Kahlmann*, Catharina C Moor*, Sanne J van Helmond,
Rémy L M Mostard, Marije L van der Lee, Jan C Grutters,
Marlies S Wijsenbeek°, Marcel Veltkamp°

1. Center of Excellence for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
2. ILD Center of Excellence, Department of Pulmonology, St. Antonius Hospital, Nieuwegein, the Netherlands
3. Department of Respiratory Medicine, Zuyderland Medical Center, Heerlen, the Netherlands
4. Helen Dowling Institute, Scientific Research Department, Bilthoven, the Netherlands.
5. Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands
6. Department of Medical and Clinical Psychology, Center of Research on Psychology in Somatic diseases (CoRPS), Tilburg University, Tilburg, the Netherlands

*These authors share first authorship

°These authors share last authorship

Abstract

Background

Sarcoidosis-associated fatigue is highly prevalent and is often reported as the most burdensome symptom of sarcoidosis. Management of fatigue is challenging, and evidence-based therapies are lacking. In this TIRED trial, we aimed to assess the effects of a 12-week online mindfulness-based cognitive therapy (eMBCT) on fatigue.

Methods

This study was a prospective, open-label, multicentre randomised controlled trial, conducted at three centres in the Netherlands. Eligible patients were 18 years or older, had stable sarcoidosis, and a score of more than 21 points on the Fatigue Assessment Scale (FAS). Patients were randomised into either the eMBCT or the control group. Participants completed patient-reported outcome measures at baseline, after intervention (T1), and 12 weeks after completion of eMBCT (T2). The primary outcome was the change in FAS score at T1 in the eMBCT group compared with the control group, assessed with the independent students' t test in all patients who started the study. Secondary outcomes included within-group difference in FAS score at T1 and T2, between-group difference in FAS score at T2, and changes in the Hospital Anxiety and Depression Scale, the Freiburg Mindfulness Inventory–Short Form, and the Kings Sarcoidosis Questionnaire. The study was registered at the Netherlands Trial Register, NL7816.

Findings

Between June 5, 2019, and Oct 28, 2021, 99 patients were randomly assigned to the eMBCT (n=52) or the control (n=47) groups. Six patients withdrew consent after psychological screening before the start of eMBCT. Baseline FAS score was similar in both groups (34.57 [SD 6.07] for 46 patients in the eMBCT group and 35.51 [4.65] for 47 patients in the control group). Mean change in FAS score at T1 was –4.53 (SD 5.77; $p < 0.0001$) in the eMBCT group and –1.28 (3.80; $p = 0.026$) in the control group (between-group difference 3.26 [95% CI 1.18 to 5.33; $p = 0.0025$]). Furthermore, the eMBCT group had a significant improvement in anxiety (mean between-group difference 1.69, 95% CI 0.22–3.16; $p = 0.025$), depressive symptoms (1.52, 0.08–2.95; $p = 0.039$), mindfulness (3.1, 0.70–5.49; $p = 0.022$), and general health status (6.28, 2.51–10.06; $p = 0.002$) at T1, compared with the control group.

Interpretation

12 week eMBCT improves fatigue, anxiety, depression, mindfulness, and health status in patients with sarcoidosis-associated fatigue.

Funding

Dutch Sarcoidosis Patient Association (Sarcoidose.nl).

Introduction

Sarcoidosis is a multisystem, granulomatous disorder of unknown cause that can affect any organ and most commonly occurs in adults aged 40–60 years (1). Fatigue is reported in up to 90% of patients with sarcoidosis and is often described as its most burdensome symptom (2,3). Fatigue negatively affects health-related quality of life and reduces social participation and work ability (4–6). The cause of sarcoidosis-associated fatigue is complex: physical, psychological, and behavioural factors could have a role in the onset and persistence of fatigue (7). Sarcoidosis-associated fatigue poorly correlates with disease severity and clinical parameters, and often persists even when there are no signs of active granulomatous inflammation (4,8). Although the substantial burden of fatigue is well known, studies investigating treatment options are scarce. The importance of investigating new management strategies to improve quality of life in patients with sarcoidosis was highlighted by a multidisciplinary group of sarcoidosis experts (9).

Prospective cohort studies and small randomised control trials (RCTs) have suggested short-term benefits from inpatient and outpatient pulmonary rehabilitation and physical training programmes on fatigue (10–13). Larger RCTs are needed to confirm and validate these findings. Some small RCTs showed that neurostimulants, such as methylphenidate and armodafinil, or steroids, such as dexamethasone, could have the potential to improve sarcoidosis-associated fatigue; however, generalisability of these results is limited by the small sample size (14–16).

Several studies have shown that psychological symptoms, such as anxiety, depression, cognitive impairment, and stress are strongly associated with fatigue (17–20). Two small pilot studies investigated the effect of psychological interventions on fatigue and psychological wellbeing in patients with sarcoidosis (21,22). A single session of 45-min mindfulness training improved physical and psychological symptoms, including fatigue, in 26 participants (22). Another small pilot study in 14 patients showed that a 6-week group cognitive behavioural therapy improved fatigue after a 1-year follow-up (21).

An online mindfulness-based cognitive therapy (eMBCT) has previously been developed for the treatment of fatigue in patients with cancer. This eMBCT program aims to change maladaptive automatic cognitive reactions and behaviour towards stressors in patients, including the fatigue itself. An RCT

showed that eMBCT improved fatigue in patients with cancer compared with active controls (23). Subsequently, the eMBCT program has been adapted for patients with chronic diseases in general.

In this Trial of a Web-based Psychological Intervention to Reduce Stress and Fatigue in Patients with Sarcoidosis (TIRED), we aimed to investigate whether a 12-week eMBCT program reduces fatigue in patients with sarcoidosis. Our secondary aims were to assess the effects of eMBCT on psychological symptoms and health status, and its long-term effects.

Research in context

Evidence before this study

Fatigue in patients with sarcoidosis is highly prevalent and reported in up to 90% of patients. Fatigue is associated with psychological symptoms, such as anxiety, depression, and stress in a bidirectional way. Mindfulness-based cognitive therapy has been found to be an effective treatment to improve fatigue in other chronic disorders.

We searched PubMed using the terms “sarcoidosis”, “psychological intervention”, “mindfulness”, “cognitive behavioural therapy”, and “fatigue” for articles published up to March 1, 2022. No language restrictions were used. References lists of articles were screened for additional manuscripts. This search retrieved only two low-quality, small pilot studies. One study suggested that a 45-min single session of mindfulness-based training could improve fatigue in sarcoidosis, and one cohort study in 14 patients indicated that cognitive behavioural therapy improves fatigue in patients with sarcoidosis.

Added value of this study

Our results show that online mindfulness-based cognitive behavioural therapy (eMBCT) improves fatigue, anxiety, depression, mindfulness, and health status in patients with sarcoidosis-associated fatigue. The beneficial effects persisted during follow-up 12 weeks after completion of the eMBCT program.

Implications of all the available evidence

To our knowledge, this study is the first large randomised controlled trial investigating the effect of eMBCT on fatigue in patients with sarcoidosis. As the 12-week eMBCT program is online, it can easily be implemented in clinical care for patients with

Methods

Study design and participants

This study was a non-blinded, multicentre, RCT conducted in three hospitals in the Netherlands. Eligible patients were adults (>18 years) diagnosed with sarcoidosis according to the American Thoracic Society, European Respiratory Society, and the World Association for Sarcoidosis and Other Granulomatous Disorders criteria guidelines (24,25), who had fatigue, unchanged sarcoidosis-related therapy during the past 8 weeks before inclusion and stable disease according to the treating physician. Fatigue was defined as a score of more than 21 points on the Fatigue Assessment Scale (FAS) (26). Patients were excluded if they had no access to the internet, were unable to read or write in Dutch, were currently under treatment of a psychiatrist or psychologist, or were participating in a physical rehabilitation programme. All patients with sarcoidosis who presented with symptoms of fatigue were invited to participate in this trial by their treating physician. All patients provided written informed consent to participate in this trial. Approval was obtained from the medical ethics committee of the Erasmus Medical Center and local ethics committees.

Randomisation and masking

In this open-label trial, patients were randomised with the permuted block technique using an online allocation program in a 1:1 ratio to receive eMBCT (intervention group) or standard care (control group). Randomisation was stratified by centre and use of anti-inflammatory medication. Patients in the control group were placed on a waiting list and could start the eMBCT treatment after completion of the study.

Patients randomised into the intervention group were referred for eMBCT to the Helen Dowling Institute, a mental health-care institution specialised in the psychological treatment of fatigue in cancer and chronic diseases. Before the start of the eMBCT, patients had a phone interview with a psychologist at the Helen Dowling Institute to discuss eMBCT in more detail and to define treatment goals. After this interview, patients could then decide if they were willing to start with the eMBCT. In practice, however, it turned out that this led to higher drop-out in the intervention group compared with the control group. After the inclusion of 44 patients, we started referring all patients for the intake interview with the psychologist before randomisation. Furthermore, we decided to change the randomisation strategy to a 3:2 ratio for receiving eMBCT or standard care. The randomisation module was converted after inclusion of the 56th patient.

Procedures

eMBCT is a comprehensive program, which consists of eight sessions during approximately 12 weeks (**appendix**). Patients had access to a secured online platform on which they received written information about a specific theme each week and kept a diary during the week to reflect on general wellbeing, stress, and fatigue. Furthermore, they could practice series of mindfulness exercises. Patients were asked to practice mindfulness for approximately 30 min each day, at least 6 days per week, and documented their experiences with this routine in their personal log. For example, patients could write down when they felt tired, what their thoughts and feelings were at that moment, and how they reacted. For the mindfulness exercises patients had audio files to guide them. The exercises comprised topics, such as relaxation, eating with awareness, moving with awareness, 3-min breathing exercises, or meditation. Apart from the intake interview, communication was mostly asynchronous: the therapist read the experiences in the logs and wrote feedback once a week. A psychologist gave personalised feedback to the experiences patients described; this feedback could be emphatic utterances probing self-reflection, informing, psycho-education, task prompting, paraphrasing, task reinforcement, providing group context, and alliance bolstering (27). The eMBCT program was considered completed as per protocol if at least six of eight sessions were followed within 6 months.

Both study groups had hospital visits at baseline (T0), after completion of the eMBCT program (eMBCT group) or at 12 weeks (control group; T1), and 12 weeks later (T2). For the eMBCT group the timing of T1 could vary as the eMBCT was completed at patients' own pace with a guidance of 12 weeks. Patients were asked to complete online patient-reported outcomes measures at all-time points before the hospital visit.

Outcomes

The primary outcome of this study was the between-group difference in change of the FAS at T1. If patients did not complete baseline questionnaires, FAS data at screening were used. The FAS is a validated self-reporting questionnaire to measure fatigue in patients with sarcoidosis.²⁶ The FAS consists of ten questions: five questions about mental fatigue and five about physical fatigue. Questions are answered on a 5-point Likert scale; scores range from 10–50 with high scores indicating worse fatigue. A score of more than 21 indicates fatigue and more than 34 indicates severe fatigue. The minimal clinically important difference is 4.0 points or a 10% difference (28,29).

Secondary endpoints included within-group difference in FAS score at T1 and T2; between-group difference in change in FAS score at T2; within and between-group difference in scores of the King's Sarcoidosis Questionnaire, the Hospital Anxiety and Depression Scale, and the Freiburg Mindfulness Inventory–Short Form at T1 and T2. The King's Sarcoidosis Questionnaire is a validated questionnaire to assess health status in patients with sarcoidosis. It comprises 29 items in five subdomains (i.e., general health status, lungs, eyes, skin, and medication). Scores of all subdomains range from 0–100; a high score represents a better health status than a low score. The minimal clinically important difference for the King's Sarcoidosis Questionnaire general health status is 8 points (30). The Hospital Anxiety and Depression Scale is a self-reporting questionnaire to assess anxiety and depressive symptoms. Scores range from 0–21, with the cut-off point for either anxiety or depressive symptoms being 8 points. The minimal clinically important difference for sarcoidosis is unknown; in patients with chronic obstructive pulmonary disease the minimal clinically important difference is 1.6 for both anxiety and depressive symptoms (31). The Freiburg Mindfulness Inventory–Short Form was developed to measure a patient's perceived mindfulness during the past 7 days. This questionnaire consists of 14 questions answered on a 4-point Likert scale. Scores range between 14 and 56; high scores indicate a greater mindfulness level than a low score (32). The Dutch translation was validated in populations who are medically ill: patients with cardiovascular disease and severely fatigued survivors of cancer (33).

Furthermore, visual analogue scales were compared at T0, T1, and T2 and patient satisfaction with eMBCT was assessed, which will be reported elsewhere. Hair samples were collected to measure hair cortisol levels at T0 and T1. Blood samples were collected for exploratory analysis of potential biomarkers including angiotensin-converting enzyme and serum soluble interleukin-2 receptor at T0 and T1. The outcomes of the hair cortisol measurement and explorative analyses of blood samples are not yet available and will be analysed and published separately. Correlation between fatigue, serum soluble interleukin-2 receptor, and hair cortisol will also be analysed later and reported elsewhere.

Statistical analysis

We calculated that with a sample size of 112 patients the study would have 80% power to detect a clinically significant difference of 4 points in the FAS score between the intervention and control group. Sample size calculation was based on observational data from Strookappe and colleagues (11), who found a SD of change in the FAS score of 7.5 points after a 3-month physical rehabilitation programme.

Between-group differences in change in patient-reported outcomes measures at T1 and T2 were tested with the Independent Students' t tests in all patients assigned to the control group and all patients who started eMBCT. We additionally performed complete case analyses, as we were only able to calculate within and between-group differences if data were available at baseline and T1. For the primary endpoint, we also performed post-hoc analyses to adjust for potential confounding factors. An analysis of covariance (ANCOVA) was performed on the change from baseline in FAS, with medication use, centre, treatment, and randomisation period as factors, and baseline FAS as covariate. Interactions between treatment and centre and between randomisation period and treatment were also investigated. Non-significant interactions were removed from the final analysis. From this model the least-squares means were derived and used to evaluate the difference between both groups. To evaluate a potential effect of missing data, we performed post-hoc sensitivity analyses in which we imputed a conservative mean change of 0 for all patients with missing data at T1. Within-group differences in patient-reported outcome measure scores over time were analysed with paired t tests. The effect size was calculated with the Cohen's d test. Effect sizes are classified as small ($d=0.2-0.49$), medium ($0.5-0.79$), or large (≥ 0.8). The proportion of patients with clinically relevant improvement in their FAS score at T1 was compared between groups with χ^2 tests. Finally, a relative risk for clinically relevant improvement was calculated.

Data are described as mean (SD) or median (IQR), if non-normally distributed. We also performed the primary analysis in the per-protocol population (as a post-hoc analysis) of patients who completed at least six of eight sessions within 6 months (eMBCT group) or who didn't change treatment (control group). $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS (version 21) and SAS (version 9.4).

Role of the funding source

We conceived the idea for the study together with the funder (the Sarcoidosis Patient Association). The funder of the study had no role in the study design, data collection, analysis, interpretation of the data, writing the report, or decision to submit the paper for publication. This study was registered at the Netherlands Trial Register (NL7816).

Results

Between June 5, 2019, and Oct 28, 2021, 214 patients were assessed for eligibility (**Figure 1**). Data analysis was performed after the inclusion of 99 patients because capacity problems of the Helen Dowling Institute, due to the COVID-19 pandemic, which resulted in a temporary halt to patient intake. As this analysis showed a positive result, we decided to stop further study inclusion. 39 (18%) patients did not meet inclusion criteria and 76 (36%) of 214 patients declined to participate. 52 (53%) of 99 patients were assigned to the eMBCT group and 47 (47%) patients were assigned to the control group. In the eMBCT group, six (12%) patients withdrew consent after psychological screening before the start of eMBCT and were excluded from the all analysis.

Mean age was 50.40 years (SD 11.03), 55 (59%) of 93 patients were female, and 29 (31%) of 93 were currently using immunosuppressive treatment (**Table 1**). Mean FAS score was 35.04 (SD 5.39) and 48 (52%) of 93 patients had severe fatigue. In patients who completed the eMBCT, median duration of the program was 14.57 weeks (IQR 8.71). No study-related adverse events were reported.

Baseline FAS score was similar in both groups (35.51 [SD 4.65] for the control group and 34.57 [6.07] for the eMBCT group). Patients in the eMBCT group had lower FAS scores at T1 than the control group: between-group difference in change was 3.26 points (95% CI 1.18 to 5.33; $p=0.0025$). In the intervention group, there was a clinically and statistically significant improvement in FAS score from T0 to T1; mean change was -4.53 (SD 5.77; $p < 0.0001$). The effect size was medium ($d=0.79$). In the control group, the mean change in FAS score was -1.28 (3.80; $p=0.026$), which was not clinically meaningful (**Figure 2**).

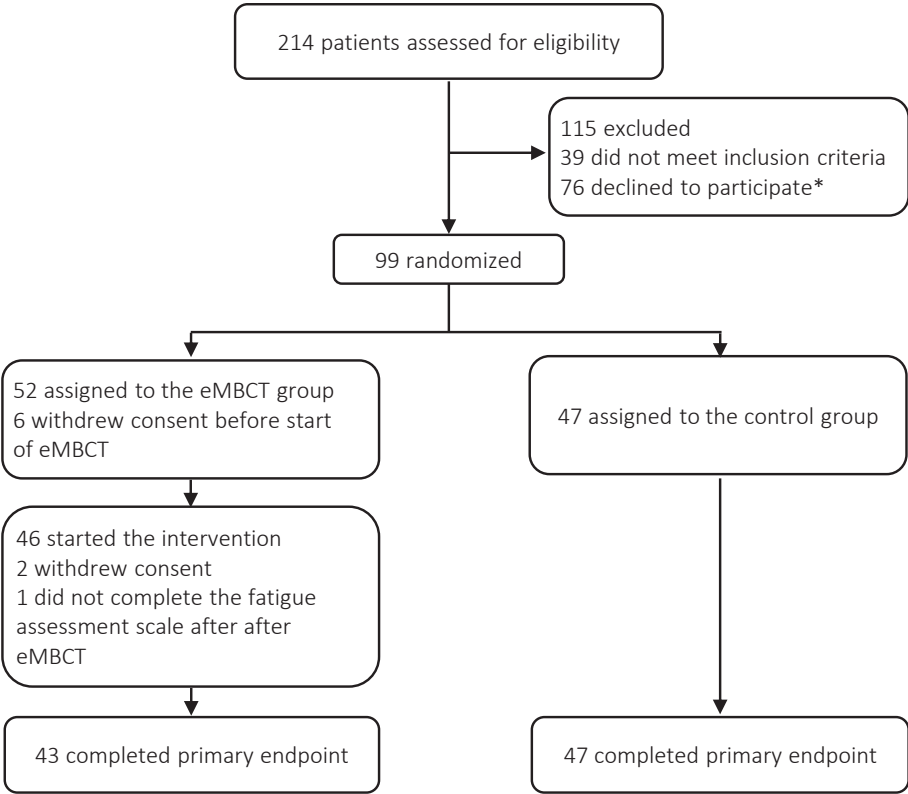


Figure 1. Trial profile
eMBCT=online mindfulness-based cognitive behavioural therapy. FAS=fatigue assessment scale. *Different reasons included logistical reasons, not fatigued according to patient’s own judgement, and programme not attractive.

Table 1: Baseline characteristics

	Total (n=93)	eMBCT (n=46)	Control (n=47)
Sex			
Male	38 (40.9%)	21 (45.7%)	17 (36.2%)
Female	55 (59.1%)	25 (54.3%)	30 (63.8%)
Age, years	50.40±11.03	50.43±10.30	50.36±11.82
Self-reported ethnicity			
White	85 (91.4%)	41 (89.1%)	44 (93.6%)
Black	1 (1.1%)	0	1 (2.1%)
Surinamese Hindi	3 (3.2%)	1 (2.2%)	2 (4.3%)
Other	4 (4.3%)	4 (8.7%)	0
Smoking status			
Current	5 (5.4%)	2 (4.3%)	3 (6.4%)
Former	32 (34.4%)	20 (43.5%)	12 (25.5%)
Never	56 (60.2%)	24 (52.2%)	32 (68.1%)
Disease duration			
<2 years	27 (29.0%)	11 (23.9%)	16 (34.0%)
2-5 years	29 (31.2%)	14 (30.4%)	15 (31.9%)
>5 years	37 (39.8%)	21 (45.7%)	16 (34.0%)
Immunosuppressive medication			
Yes	29 (31.2%)	15 (32.6%)	14 (29.8%)
No	64 (68.8%)	31 (67.4%)	33 (70.2%)
Pulmonary function tests			
FVC % predicted (n=50)	97.80±12.06	96.74±13.38	98.70±10.99
DLCO % predicted (n=43)	81.56±13.19	84.10±14.83	79.14±11.21
Serum biomarkers			
Soluble interleukin 2 receptor (pg/ml) reference value <2500 pg/ml (n=81)	3128±1643	3322±2033	2965±1225
Angiotensin converting enzyme (U/L), reference value 12-82U/L (n=71)	50.45±21.97	52.46±24.91	48.98±19.73

Table 1: Continued

	Total (n=93)	eMBCT (n=46)	Control (n=47)
Organ involvement*			
Lymphadenopathy	81 (87.1%)	42 (91.3%)	39 (83.0%)
Lungs	64 (68.8%)	31 (67.4%)	33 (70.2%)
Eyes	10 (10.8%)	9 (19.6%)	1 (2.1%)
Skin	9 (9.7%)	2 (4.3%)	7 (14.9%)
Heart	5 (5.4%)	4 (8.7%)	1 (2.1%)
Liver	6 (6.5%)	1 (2.2%)	5 (10.6%)
Spleen	4 (4.3%)	0	4 (8.5%)
Muscles/bones/joints	9 (9.7%)	5 (10.9%)	4 (8.5%)
Central nervous system	1 (1.1%)	1 (2.2%)	0
Gastro-intestinal	1 (1.1%)	0	1 (2.1%)
Renal	3 (3.2%)	2 (3.2%)	1 (2.1%)
Fatigue Assessment Scale	35.04±5.39	34.57±6.07	35.51±4.65
Fatigue	45 (48.4%)	22 (47.8%)	23 (48.9%)
Severe fatigue	48 (51.6%)	24 (52.2%)	24 (51.1%)
Hospital Anxiety and Depression Scale			
Anxiety (n=84)	7.95±4.05	7.54±4.2	8.28±3.94
Depression (n=84)	7.80±4.3	7.57±4.8	7.98±3.9
Freiburg Mindfulness Inventory (n=84)	35.65±7.44	35.67±7.66	35.64±7.34
King's Sarcoidosis Questionnaire			
General Health (n=84)	48.64±10.21	49.73±11.19	47.79±9.4

In the post-hoc ANCOVA, we found no effect of treatment centre, medication, and randomisation period on outcomes (appendix 2). Baseline FAS and intervention group were the only significant factors in the model. In the full model without non-significant interactions, the difference in change from baseline to T1 in least-squares means between both groups was 3.62 (95% CI 1.61 to 5.64; p=0.0006). In the intervention group, mean change in FAS score was -4.47 points (95% CI -6.32 to -2.63; p=0.037); in the control group, FAS score did not significantly change (-0.85 points; 95% CI -2.67 to 0.98; p=0.690). Post-hoc sensitivity analyses with missing data at T1 imputed with a conservative mean change of 0 (n=9) did not significantly differ from the complete case analyses, the least squares mean difference between both groups was 2.59 points (95% CI 0.69 to 4.49; p=0.008; appendix 2). The improvement in FAS score in the eMBCT

group seemed to persist during long-term follow-up: mean change was -3.95 (SD 6.40; p=0.0003) between T0 and T2. In the control group, FAS scores improved between baseline and T2, mean change was -1.93 (3.01; p<0.0001), which was not clinically meaningful. The between-group difference in change of FAS score between T0 and T2 was 2.02 points (95% CI -0.16 to 4.20; p=0.068; Figure 2).

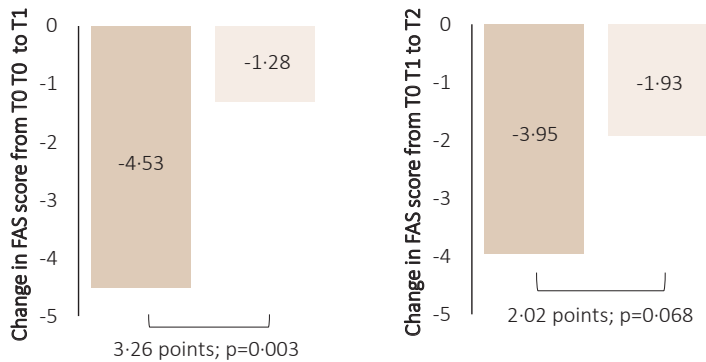


Figure 2. Mean change in FAS scores (A) Mean change in FAS score from T0–T1. (B) Mean change in FAS scores from T0–T2. As within-group differences in the eMBCT and control group were rounded, they do not exactly match between-group differences. eMBCT=online mindfulness-based cognitive therapy. FAS=fatigue assessment scale. T0=before starting eMBCT or after randomisation for controls. T1=after completion of the eMBCT program (eMBCT group) or at 12 weeks (control group). T2=12 weeks after completion of eMBCT and 12 weeks after T1 for the control group.

In the eMBCT group, more patients had a clinically relevant improvement in fatigue score at T1 compared with the control group (26 [60%] of 43 vs 12 [26%] of 47; p=0.0008; Figure 3). Patients in the eMBCT group were more likely to have clinically relevant improvement in fatigue when compared with the control group (relative risk [RR] 2.37; 95% CI 1.37–4.08). The improvement of fatigue score in the eMBCT group persisted during follow-up (20 [48%] of 42 vs 11 [25%] of 44; p=0.029).

At baseline, 84 patients completed the Hospital Anxiety and Depression Scale; prevalence of anxiety was 52% (mean score 7.95 [SD 4.05]), and depressive symptoms was 51% (mean score 7.80 [SD 4.3]). Patients in the eMBCT group had significantly more improvement in anxiety (between-group difference 1.69; 95% CI 0.22 to 3.16; p=0.025) and depressive symptoms (1.52; 0.08 to 2.95; p=0.039) compared with the control group, which persisted during follow-up.

Table 2: Secondary endpoints

	eMBCT group	Control group	Between-group difference (95% CI)
HADS anxiety			
Change at T1 (n=82)	-1.94±3.70; p=0.004	-0.26±2.63; p=0.508	1.69 (0.22 to 3.16); p=0.025
Change at T2 (n=78)	-2.03±3.61; p=0.002	0.36±2.73; p=0.382	2.39 (0.97 to 3.82); p=0.001
HADS depression			
Change at T1 (n=82)	-2.2±3.69; p=0.001	-0.68±2.86; p=0.109	1.52 (0.08 to 2.95); p=0.039
Change at T2 (n=78)	-2.35±3.69; p<0.001	-0.16±2.83; p=0.711	2.19 (0.72 to 3.66); p=0.004
FMI			
Change at T1 (n=82)	3.54±7.06; p=0.005	0.45±3.7; p=0.412	3.10 (0.70 to 5.49); p=0.022
Change at T2 (n=77)	4.56±6.80; p<0.001	-0.72±5.09; p=0.358	5.28 (2.58 to 7.98); p<0.001
KSQ general health			
Change at T1 (n=83)	7.16±9.78; p<0.001	0.88±6.50;p=0.358	6.28 (2.51 to 10.06); p=0.002
Change at T2 (n=78)	8.11±9.90; p<0.001	2.14±6.95; p=0.047	5.97 (2.17 to 9.77); p=0.002

In the control group, anxiety and depressive symptoms remained unchanged (Table 2). In the intervention group, a significant improvement in health status and mindfulness score was found compared with the control group (Kings Sarcoidosis Questionnaire between-group difference 6.28; 2.51 to 10.06; p=0.002 and Freiburg Mindfulness Inventory–Short Form 3.10; 0.70 to 5.49; p=0.022). At T2, Kings Sarcoidosis Questionnaire and Freiburg Mindfulness Inventory–Short Form scores were higher than at T1.

In the eMBCT group, 36 (78%) of 46 patients attended at least six of the eight sessions within 6 months and were included in the per-protocol analysis. In the control group, 45 (96%) of 47 patients were included in the per-protocol analysis (two patients were excluded due to change in treatment with methylphenidate). In the per-protocol analysis, patients in the eMBCT group had a larger improvement in fatigue scores at T1 compared with the control group (between-group difference in change was 3.88 points; 95% CI 1.56 to 6.20; p<0.001), which exceeded the minimal clinically important difference of more than 10% difference. In the eMCBT group, there was a significant and clinically relevant improvement in FAS scores at T1 (mean change –5.17 [SD 5.97; p<0.001]). In the control group, the mean change in FAS score was –1.29 (SD 3.79; p=0.028), which was not clinically meaningful. The between-group difference in change in FAS scores at T2 was 2.40 points (95% CI –0.05 to 4.84; p=0.055), favouring the eMBCT group (mean change 4.32 [SD 6.52; p<0.001]).

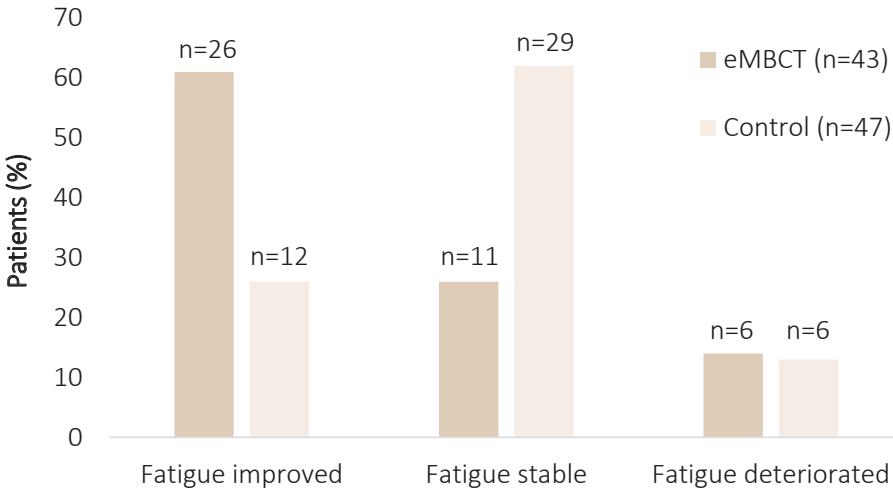


Figure 3. Proportion of patients in each group with improved, stable, or deteriorated FAS score at T1

Discussion

To our knowledge, this study is the first RCT investigating the effect of eMBCT on sarcoidosis-associated fatigue. A 12-week eMBCT program improved fatigue in patients with sarcoidosis. Moreover, anxiety, depression, mindfulness, and health status improved after eMBCT. Beneficial effects within the intervention group persisted 12 weeks after completion of the eMBCT program.

Until now, data on the effects of psychological interventions on fatigue in sarcoidosis have been scarce (21,22). In our study, the mean improvement in FAS score in the eMBCT group was clinically relevant and persisted over time. Between-group differences were statistically significant, and the proportion of patients with improved fatigue was higher in the eMBCT group (60%) versus the control group (26%). These results are in concordance with the effect of eMBCT seen in patients with other chronic disorders (23,34). The marginal non-clinically relevant increase in FAS score seen in the control group could be due to the extra attention paid to fatigue during study visits and completing questionnaires at home. We speculate that, even in the control group, this attention could have led to increased insights into fatigue and better self-management.

Previous studies on physical activity-based modalities in patients with sarcoidosis showed a positive effect on fatigue directly after the intervention (10–13). Nevertheless, physical-based modalities might not be feasible in all patients with sarcoidosis, as illustrated by previous studies, highlighting the need for more personalised tailored treatment options. The best treatment option for fatigue could depend on the underlying determinants of fatigue. Patients suffering from physical fatigue might benefit most from physical-based modalities, whereas patients with mental fatigue might benefit more from psychological interventions, and in other patients a combined treatment might be the best treatment option. To provide better individually targeted treatment in the near future, research is needed to investigate the factors that predict treatment success, both for psychological and physical activity-based interventions.

Psychological symptoms, such as anxiety, depression, or stress have been reported in up to 30–60% of patients with sarcoidosis (7), which is in line with the 50% of patients in our study with anxiety and depressive symptoms. This proportion indicates the need for structural screening and better management of these burdensome symptoms. Our study showed a statistically and clinically meaningful improvement in anxiety and depression scores in the eMBCT group.

However, notably we extrapolated the minimal clinically important difference from chronic obstructive pulmonary disease, as it has not yet been established for sarcoidosis. Whether eMBCT is also effective in patients with sarcoidosis without fatigue, who experience symptoms of stress, anxiety, and depression, seems plausible, but remains to be elucidated. Moreover, as cognitive dysfunction and physical inactivity are also frequently reported problems in sarcoidosis, measuring the effects of mindfulness-based therapies on cognitive functioning and physical activity in future studies, could further expand our knowledge of the cause of sarcoidosis-associated fatigue (17).

Notably, patients reported an improvement in health status, as measured by the King's Sarcoidosis Questionnaire directly after the eMBCT program, and these beneficial effects further improved during long-term follow-up. To our knowledge, this RCT is the first intervention study in sarcoidosis showing an improvement in health status measured by the King's Sarcoidosis Questionnaire after treatment. This result shows that the King's Sarcoidosis Questionnaire is a responsive measure in patients with sarcoidosis, and its use in future studies to assess the effects of pharmacological and non-pharmacological interventions on health status is promising.

In our study, 36% of the approached patients declined to participate at screening, and another six patients in the eMBCT group declined to participate after the psychological intake visit. The main reasons for decline were that patients thought the program was too time consuming or did not appreciate its content. For some patients, negative associations and preconceptions with mindfulness also played a role in the decision to decline eMBCT. Of the patients who started eMBCT, 78% completed the program per protocol, which is higher than a previous trial investigating eMBCT in patients with cancer and fatigue (23). Since we found a larger positive effect on fatigue in the group that completed the eMBCT program (per-protocol analysis), thorough patient education and selection beforehand could maximise effects.

As eMBCT is reimbursed in the Netherlands for patients suffering from a somatic symptom disorder, such as severe chronic fatigue, it can be easily implemented in clinical care for patients with sarcoidosis. However, reimbursement can vary per country. We chose an online MBCT program because this format lowered the burden for patients to participate, especially for patients with severe fatigue that considerably affects their daily lives. In this eMBCT program, patients did not have to travel to see a psychologist and could follow the sessions at their

own pace. Moreover, as distances are bridged online, this program will facilitate implementation, allowing patients throughout the country to participate. Nevertheless, the program can also be offered face-to-face, so treatment could be personalised to individual patient wishes, irrespective of digital literacy.

Strengths of this study include the large multicentre study sample with a heterogeneous group of patients with sarcoidosis and the long-term follow-up. This study also had some limitations. We prematurely stopped the study due to capacity problems caused by the COVID-19 pandemic and changed the randomisation strategy from 1:1 to 3:2 as we noticed a higher drop-out in the intervention group directly after psychological screening (ie, before the start of the eMBCT). Nevertheless, post-hoc analyses suggested that this adjustment did not influence our results and conclusions. Designing an RCT to assess the effect of a psychological-based intervention, like our study, has inherent complexities, such as whether to use a sham group or not. We opted for a waiting list control instead of a sham comparator group. A systematic review and meta-analysis on the effects of mindfulness-based therapy in survivors of cancer indicated that there were no differences in outcomes when comparing regular control groups with a sham comparator group (35). Moreover, we did discuss fatigue, anxiety, depression, and health status in our control group during study visits, to treat both study groups as equal as possible. These discussions might have led to a higher degree of activation for self-management in the control group, causing an underestimation of between-group differences at the expense of the eMBCT group. Also, the investigators were not blinded, although we do not think this fact influenced outcomes as patients filled-out questionnaires at home before the study visits. Finally, to reflect daily clinical practice, the duration of the treatment was variable depending on patients' preferences. Nevertheless, we do believe these changes have not affected our results and conclusions. In summary, this multicentre RCT showed that 12-week eMBCT improved sarcoidosis-associated fatigue. We conclude that eMBCT is an effective treatment for fatigue in patients with sarcoidosis and can be easily integrated into daily practice.

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Supplementary appendix

Supplement 1: Modules of the online mindfulness-based cognitive program

eMBCT is a comprehensive program, which consists of eight sessions during approximately 12 weeks. All modules consist of psycho education and exercises. In the current study, patients had access to a secured online platform where they received written information about a specific theme each week, kept a diary during the week to reflect on general wellbeing, stress, and fatigue. Furthermore, they could practice series of mindfulness exercises. Patients were asked to practice mindfulness for approximately 30 minutes each day, at least six days per week and documented their experiences with this in their personal log. For example, patients could write down what their thoughts and feelings were at that moment and how they reacted to this feeling. For the mindfulness exercises, patients had audio files to guide them. The exercises comprised topics, such as relaxation, eating with awareness, moving with awareness, 3-minutes breathing exercises, or meditation. Apart from the intake interview, communication was mostly asynchronous: the therapist read the experiences in the logs and wrote feedback once a week.

Intake interview

Before the start of eMBCT patients were asked to fill out a standard intake form on a webpage, as part of regular care. The intake form included demographic information, medical history, reasons for application, illness and recent physical complaints, previous (psychological) care, coping, social support, and questionnaires about anxiety/depression and fatigue. Hereafter, patients had an interview with a psychologist to discuss the intake form and also the content of the eMBCT program. This intake session was used as a diagnostic assessment, to examine patients' complaints, symptoms and needs. In addition, coping mechanisms and perpetuating factors were also addressed, as well as strengths, traumas, and how the patient copes with boundaries. Subsequently, a treatment plan was developed.

Module 1 - Fatigue and the automatic pilot

This is the start of the eMBCT program. In this module, patients define treatment goals and receive psychoeducation about fatigue, coping with stress, and 'the automatic pilot'. The module starts by stating that "A large part of the time we live on automatic pilot, as if we drive in a car for several kilometers without really being aware of what we are doing. In these moments we are not consciously

aware, and we act according to our habits. By devoting more attention to your body and feelings, you will be better able to cope with your fatigue." Patients practice relaxation and awareness of the body with an audio file 'the bodyscan' – They register their experiences with the "the bodyscan" and register experiences with eating with awareness. This module comes with audio of a 32-minute body scan exercise.

Module 2 – Practice open-minded

In this module, patients receive psychoeducation about coping with a chronic disease, pain, and fatigue. Furthermore, they receive information about handling thoughts during breathing exercises and tips for better sleep quality. The exercises focus on the ability to observe things in the moment and increase awareness of bodily responses during specific situations. Patients will learn step by step to accept each situation as it is, with an open mind, without judging themselves or their situation. The exercises help the patient to increase their awareness: "The purpose is not to achieve a goal or to strive for relaxation. Simply following your breath, without changing anything, is a way to keep bringing your attention back to 'here and now'". The exercises include daily 'breathing exercise', 'body scan', awareness during a specific routine activity, and noticing thoughts and feelings during pleasant moments. Patients describe experiences with these exercises as detailed as possible in an online logbook. Additionally, patients get tips for a better sleep quality. This module comes with audio of a 22-minute body scan with muscle tension exercise, and a 14-minute attention to breathing exercise.

Module 3 – Dealing with boundaries

Module three includes recognizing unpleasant experiences and becoming aware of how one deals with physical and emotional boundaries. The program teaches patients to become increasingly aware of their own experiences. The body is used as a guide and source of information. By listening to their bodies attentively in the moment, patients learn to perceive boundaries and recognize when they are approaching or crossing a boundary: "It is not about doing the maximum, but about doing the optimal: In the optimal situation you are balanced. Train yourself to become susceptible to the signals of your body. This way, you can make better decisions." Exercises include daily registration of experiences during yoga exercises, the 'bodyscan', 'breathing exercises', 'attention for boundaries', and registering awareness of what happens when meeting boundaries. This module comes with audio of a 32-minute yoga exercise, and a 4-minute breathing exercise.

Module 4 – Dealing with stress

The module includes recognizing automatic negative cognitions, recognizing daily stress inducing experiences and their emotional impact. Patients continue to train their concentration. In this module, concentration is expanded from focusing on the body and breathing, to experiencing sounds, smells, and images. Patients will keep a diary on stressful moments and investigate under which circumstances they switch to automatic pilot. As stated in the module: “We often cannot change the circumstances we are in, but we can change the way we deal with situations. For instance, you only have the freedom to choose how to deal with stress if you notice that you are experiencing stress.” The exercises of this module help to become aware of the way tension builds up or can be released. The homework for this module includes a daily exercise of choice: ‘sitting with awareness’ or ‘walking with awareness’, alternated with previous learned exercises. Patients also register their awareness of stressful situations and write down when they notice they are shifting to automatic pilot. This module comes with audio of a 47-minute sitting meditation, and another 30-minutes sitting meditation.

Module 5 – Dealing with feelings

The module includes psychoeducation on accepting things as they are and how to cope with negative emotions through acceptance in three steps: 1. acknowledging and feeling, 2. examination of feelings, 3. which situation?. Managing feelings is the central theme: “By allowing feelings, you can let go of the things you are holding on to.” Homework includes daily exercise, including ‘accepting what is in the present’, alternated with previous learned exercises. The patient is invited to do breathing exercises a couple of times a day, especially during stressful events. Additionally, patients keep a diary of negative emotions. This module comes with audio of a 23-minute “accepting what is in the presence” exercise.

Module 6 – Dealing with thoughts and anxiety

This module includes explanation on how thoughts, behaviour and emotions interact and how one can choose to stop automatic reactions. It also addresses the physiological reactions of fear, fear of recurrence or progression of disease, and dealing with loss. This module teaches the patient that part of our thoughts arise from feelings: “If you live with a severe or chronic illness, you live with a threat. No one can tell you if or when you will go back to being your ‘old self’.” As with other thoughts, it helps to examine which thoughts you have and how realistic they are.” Concentration exercises will help the patient to live in the ‘here

and now’, decreasing their feelings of anxiety. The homework for this module includes the new exercise ‘looking at thoughts and feelings’, alternated with the previous exercises ‘breathing exercise’ and ‘accepting what is in the present’. Additionally, patients keep a diary of unhelpful, negative thoughts. This module comes with audio of a 20-minute silence exercise.

Module 7 – Self-care

In this module, the patient becomes more aware of how they can best improve their self-care: “What makes you feel good, what is important to you, and do you choose to do the things that are good for you? The things we do can have a major influence on how we feel and the way we cope with anxiety, negativity and restlessness”. Four new relaxation exercises are presented: ‘sit like a mountain’, ‘lay down like a river’, ‘relaxation breathing’, and ‘vitality breathing’. As homework, they create a personal schedule by choosing from previous exercises and test it. Additionally, patients are asked to pick a few moments and register what they want to do the most and write it down in the online ‘taking action’ log. In the log ‘taking care of myself’ they report which actions were most helpful for their self-care. Also, they are asked to keep a diary of helpful thoughts. This module comes with four audio clips of relaxation exercises.

Module 8 - From stress and fatigue to strength

This is the final module, in which the patient reflects on the program. The module includes information on going from feeling stress and fatigue to strength. Patients continue to practice the information learned during the program and create a schedule of exercises that they can continue to do without therapist feedback. They formulate potential pitfalls for the future and compose self-management strategies. Patients also reflect on what they gained from the eMBCT program and if there are any concerns with finalizing the program. In the log ‘retrospect’ they look back at what helped them during the program by answering a few questions, i.e., “Look at the goals you set at the start of the program, and evaluate whether you achieved these goals or not, or whether your goals have changed.”

Supplement 2: Post-hoc sensitivity analyses

ANCOVA model

An analysis of covariance (ANCOVA) was performed on the change from baseline in FAS, with medication use, center, treatment, and randomization period as factors, and baseline FAS as covariate. Interactions between treatment and center and between randomization period and treatment were also investigated. Non-significant interactions were removed from the final analysis. From this model the least square means (LS means) were derived and used to evaluate the difference between both groups.

	DF	Sum of Squares	Mean Square	F value	p-value
Model	6	447.385967	74.564328	3.34	0.0054
Error	83	1855.114033	22.350771		
Corrected total	89	2302.500000			

Full model without non-significant interactions:

Factor	DF	Type III SS	Mean Square	F value	p-value
Baseline FAS	1	160.9456134	160.9456134	7.20	0.0088
Center	2	41.4729596	20.7364798	0.93	0.3995
Medication	1	0.6010605	0.6010605	0.03	0.8701
Randomization period	1	0.0124254	0.0124254	0.00	0.9812
Treatment group	1	286.6370171	286.6370171	12.82	0.0006

Change in LS means Control: -0.85 points (95% CI -2.67 to 0.98); Intervention -4.47 points (95% CI -6.31 to -2.63) p=0.0006

Difference between means 3.62 points, 95% CI 1.61 to 5.64

ANCOVA model with imputation

In this model, we have imputed missing data at T1 in the intervention group (9 patients) with a mean change of 0. This is a conservative estimate as even the control group had a mean change of 1.2 points (improvement in FAS score).

In the full model without non-significant interactions, the LS mean difference between both groups was 2.59 points with a 95% CI from 0.69 to 4.49, p=0.008.

Factor	DF	Type III SS	Mean Square	F value	p-value
Baseline FAS	1	108.3697261	108.3697261	4.81	0.0308
Center	2	36.0983923	18.0491962	0.80	0.4518
Medication	1	10.4732023	10.4732023	0.47	0.4970
Randomization period	1	12.5284654	12.5284654	0.56	0.4577
Treatment group	1	164.6359750	164.6359750	7.31	0.0082

Chapter 11

Sarcoidosis and fatigue:
there is a useful cognitive
treatment? - Authors' reply



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Vivienne Kahlmann, Catharina C Moor, Marcel Veltkamp,
Marlies S Wijsenbeek, on behalf of all authors

1. Center of Excellence for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Centre, Rotterdam, the Netherlands
2. ILD Centre of Excellence, Department of Pulmonology, Saint Antonius Hospital, Nieuwegein, the Netherlands
3. Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands

Authors’ reply

We thank Roberto Carbone and colleagues for their relevant questions. The causes of fatigue are multifaceted and physical, psychological, and behavioural factors have a role in the onset and persistence of fatigue. Furthermore, treatment such as corticosteroids can also cause fatigue. We agree with Carbone and colleagues that treatable traits should be assessed and adequately managed first (**Figure**). It is important to note that many patients in our study cohort already had fatigue for a prolonged period of time (median 5.5 years, range 0.4–39.0). The majority of patients have had extensive work-up to investigate the causes of fatigue before study inclusion (1,2). In our cohort, 63 (68%) of 93 patients had one or more comorbidities, including cardiovascular disease (13%), obstructive sleep apnoea (13%), obstructive lung disease (8%), and hypothyroidism (4%). Patients could only be included if they had stable sarcoidosis and other causes of fatigue were adequately treated.

During the TIREd trial (3), the COVID-19 pandemic emerged, which had a huge impact on mental health in the general population (4). The COVID-19 pandemic could also have had a negative impact on mental health and fatigue in our study cohort. As the trial was randomised, we expect a similar effect from COVID-19 in the intervention and control group. In our study, two patients (one in each group) had COVID-19 more than 8 weeks before study start, and two patients in the intervention group reported a COVID-19 infection during the study period. Therefore, we believe that the effect of COVID-19 in our study was neglectable.

Carbone and colleagues suggested to assess fatigue in different ways. The complexity of studying fatigue is that there is no unambiguous definition of fatigue (5). Fatigue is a subjective description of the feeling of a person and often divided in a physical and mental component. The Fatigue Assessment Scale is a validated questionnaire developed for patients with sarcoidosis, including questions about physical and mental fatigue (6). Other topics suggested seem relevant, but are not yet incorporated in validated questionnaires for fatigue. As stated in our discussion, we agree that it would be interesting to include other secondary endpoints in future studies, such as physical activity and cognitive function, to increase our knowledge about fatigue in sarcoidosis. Although the effect of the 12-week online mindfulness-based cognitive therapy persisted after 3 months, we have no data beyond that. A form of maintenance online therapy could probably be beneficial for the long term.

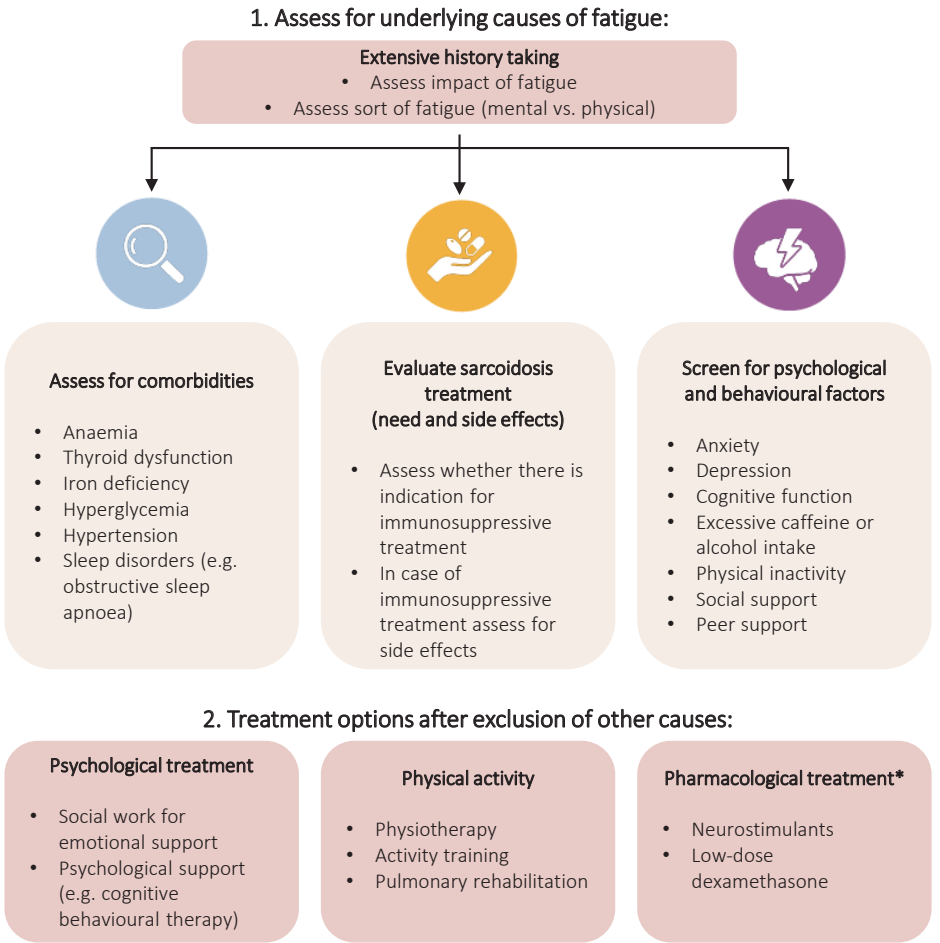
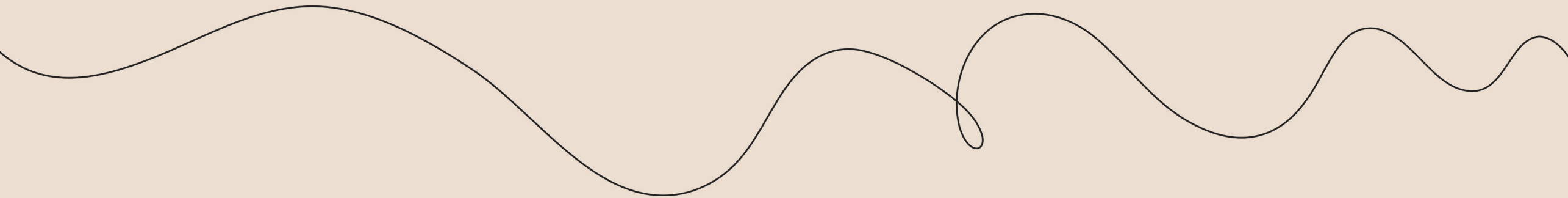


Figure. Algorithm for the assessment and management of fatigue in patients with sarcoidosis

*Limited evidence based on small cohort studies, prescribe with caution.

Chapter 12

Innovating care for people with
sarcoidosis using a machine
learning-driven approach



Vivienne Kahlmann¹, Astrid Dunweg¹, Heleen Kicken², Nick Jelacic³,
Johanna M. Hendriks⁴, Richard Goossens², Marlies S. Wijssenbeek^{1*}
and Jiwon Jung^{2,4*}

1. Centre of Excellence for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands
2. Faculty of Industrial Design Engineering, Delft University of Technology (TU Delft), Delft, the Netherlands
3. University Library, Erasmus University of Rotterdam, Rotterdam, the Netherlands
4. Surgery Department, Erasmus University Medical Center, Rotterdam, the Netherlands

*These authors share last authorship

Abstract

Introduction

Understanding patients' everyday experience is essential to improve patient centered care in sarcoidosis. So far, patient perspectives are based on survey- and qualitative research.

Aim

We aimed to assess patient-driven perspectives on their care trajectories using a novel machine learning-driven approach (MLD).

Methods

We used the largest Dutch sarcoidosis patient platform as the data source of patient stories. The patients' stories were extracted with permission. We applied topic modelling (to generate topics among the posts), and sentiment analysis (to find tone of voice in the topics). To validate the findings, we read the top 50 most relevant posts of each topic. An in-depth patients' disease trajectory map was made.

Results

Based on 4969 forum posts, 30 final topics and 10 upper themes were generated, which formed the basis for the "patient journey-map" which shows patients' perspective across the care pathway. Important decision moments could be identified, as well as care "tracks" at home and hospital and topics associated with positive or negative emotions. Most patients' perspectives were about symptoms (mainly negative sentiment), disease-modifying medication (mainly neutral sentiment), and quality of life (negative, neutral and positive).

Discussion

A major part of living with sarcoidosis takes place outside the view of the hospital, but this part often remains invisible. MLD is an innovative approach, providing a comprehensive overview of patients' perspectives on health and care. Integrating, these findings in the design of health care delivery has the potential to improve patient-centered care.

Keywords

Interstitial lung disease, Sarcoidosis, Quality of life, Artificial intelligence, Innovating care, Patient perspectives, Patient-centered care

Introduction

Sarcoidosis is a systemic inflammatory disease, most commonly affecting the lungs, but any organ can be involved. The clinical presentation of sarcoidosis is variable and the disease course often unpredictable. In most patients spontaneous remission occurs, while others require immunosuppressive treatment. Symptom burden is often high, even if there are no signs of sarcoidosis inflammatory activity (1, 2). Sarcoidosis can significantly impact daily activities, including work participation, family life and social engagement, thereby diminishing quality of life (QoL) for both patients and their families (3–5).

Understanding how people feel and function every day is essential to improve patient-centered care in sarcoidosis. As a major part of living with sarcoidosis takes place outside the view of the hospital, this part often remains invisible for healthcare providers. It is important to acknowledge that patients and healthcare providers have different views on important treatment outcomes. For patients, the most important treatment outcome is quality of life, while physicians prioritize measurements that are more physiologically oriented such as pulmonary function (6).

A few survey and qualitative studies have provided valuable information on the needs and perceptions of patients with sarcoidosis; however, these approaches did not assess patients' daily life experience data from their own narratives (3, 4, 6, 7). Furthermore, conventional qualitative studies, focus groups and interviews, are limited by sample size, labor intensive and could lead to socially desirable answers towards the interviewer. Survey studies often make use of predefined questionnaires and Likert scales and are not able to capture in-depth and extensive descriptions about the patients' struggles and needs in their daily lives.

Machine learning-driven approaches (MLD) for text modeling enable analysis of a vast collection of data. A MLD approach enables exploring non-prompted patients' experiences based on their own narratives. Moreover, the MLD approach is easily repeatable and facilitates timely updates to patient perspectives as the field evolves. In this study, we aim to assess patient-driven perspectives of patients with sarcoidosis on their care trajectories by using a MLD approach (8).

Methods

The design and conduct of this study were a collaboration between user-experience designers, data scientists, clinicians, nurses, and a patient panel. Using a MLD approach, we assessed online patient stories (8). This method consists of three steps: (I) preparation of the data, (II) MLD analysis and (III) human validation of the findings (**Figure 1**). Hereafter, we created a patient journey map, which outlines the care pathway and highlights the experiences of patients. The patient journey map was discussed during co-creation sessions with stakeholders (clinicians, specialist nurses, and a patient panel). Ethical approval was obtained by the local ethics committee.

Step 1. Preparation of data source, patient stories

We extracted anonymized patient stories from the largest online Dutch sarcoidosis patient platform, with approval from the platform owner. The online platform consisted of written patient stories without a specific format. After extraction of the forum posts, we preprocessed the data (e.g. eliminating stop words, changing all terms to lowercase, and transforming the posts into a term frequency inverse document frequency (TF-IDF) matrix). We did not make the distinction between main post and replies to the posts, because they may equally include important relevant stories from different patients.

Step 2. Analysis of patient stories by MLD approach

We used an unsupervised MLD approach called topic modeling. This is a text mining technique to classify different text documents in sets, called topics, by detecting patterns of words. We performed topic modeling with a technique called Non-negative Matrix Factorization (NMF) to find latent topics in the posts. The optimal number of topics was predefined at 40 topics, because this number of topics could be manually checked and would avoid overlapping or too wide-ranging topics. With NMF one post can relate to multiple topics with varying degrees of relatedness. Each post was assigned to the most related topic together with other related posts. Topic modelling provided the most relevant keywords and counted how many posts belonged to a specific topic. Furthermore, the 50 most relevant posts for each topic were identified and extracted, so these posts could be manually checked in step 3. Subsequently, a sentiment analysis was performed to determine to overall sentiment of the individual topics (e.g. positive, neutral, or negative). For the sentiment analysis, we used a multilingual model, XLM-RoBERTa, which was fine-tuned as outlined by Barbieri et al. (9).

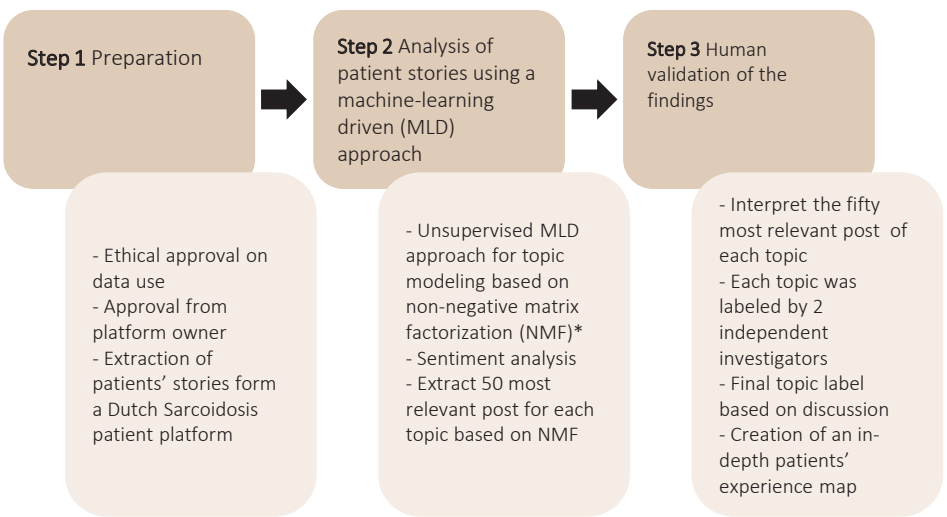


Figure 1. Stepwise methodological approach to create a patient journey map.

*Non-negative matrix factorization (NMF) as the “unsupervised machine learning technique”

Step 3. Human validation of findings

Two independent investigators (AD and HK) validated the findings by reading the keywords and 50 most relevant posts for each topic. The two investigators labeled the topics independently. When they disagreed on a label, a third investigator (VK) reviewed the topic, and the final label was agreed upon through discussion. A topic was classified as miscellaneous if no consensus could be reached after a third researcher reviewed the topic. The miscellaneous category was defined as posts within the topic being incoherent, with no identifiable main theme. Topics that were gender- or age-specific, or not related to the patient disease trajectory experience were excluded from further analysis. Similar topics were grouped into clusters.

To create the patient journey map, the topics were aligned with specific stages of the sarcoidosis care pathway. The patient journey map was reviewed during several co-creation sessions with the involved stakeholders.

Results

On December 22, 2022, we extracted 8,364 posts from the Dutch Sarcoidosis patient community platform. Figure 2 presents an overview of our study steps. The posts were created between 03-03-2008 and 12-12-2022; and were mainly written by patients and sometimes by family members. We applied topic modelling; five topics were excluded from further analysis as they were either forum specific (e.g. topic about features of the website), not related to the patient disease trajectory experience (e.g. congratulating/greeting each other) or included traceable personal data (e.g. pregnancy with sarcoidosis). The 35 relevant topics, containing 5718 posts, were labeled (Table 1). For five topics no main theme could be identified, these topics, containing 749 posts, were labeled as miscellaneous. For instance, one of these miscellaneous topics included posts on adjustments in daily life (e-bike), lifestyle interventions, vitamin B12 deficiency, and angiotensin-converting enzyme. Finally, the topics were manually clustered into 10 clusters (Figure 2).

Most frequently mentioned topics and clusters

As shown in Table 1, the most frequently mentioned topics were about symptoms (23.8%), disease modifying medication (16.0%), and impact in daily life (11.4%). Patients described general experiences about symptoms and strategies how to relieve symptoms. Furthermore, they mentioned the struggle to cope with the uncertainty of living with sarcoidosis, and questioned whether unexplained symptoms were related to sarcoidosis or not. Specifically mentioned were small fiber neuropathy and the impact of sarcoidosis on eyes and vision.

The second-largest cluster centered on disease-modifying medication. Patients shared experiences about benefits and side effects of steroids and other immunosuppressive medication. In addition, they discussed whether symptoms are likely to be caused by sarcoidosis or could be a side effect of medication. The third-largest cluster included topics on impact on daily life. Patients discussed how to keep balance in life, manage fatigue, benefits of sports and exercise and experiences with managing sleep and sleep disorders.

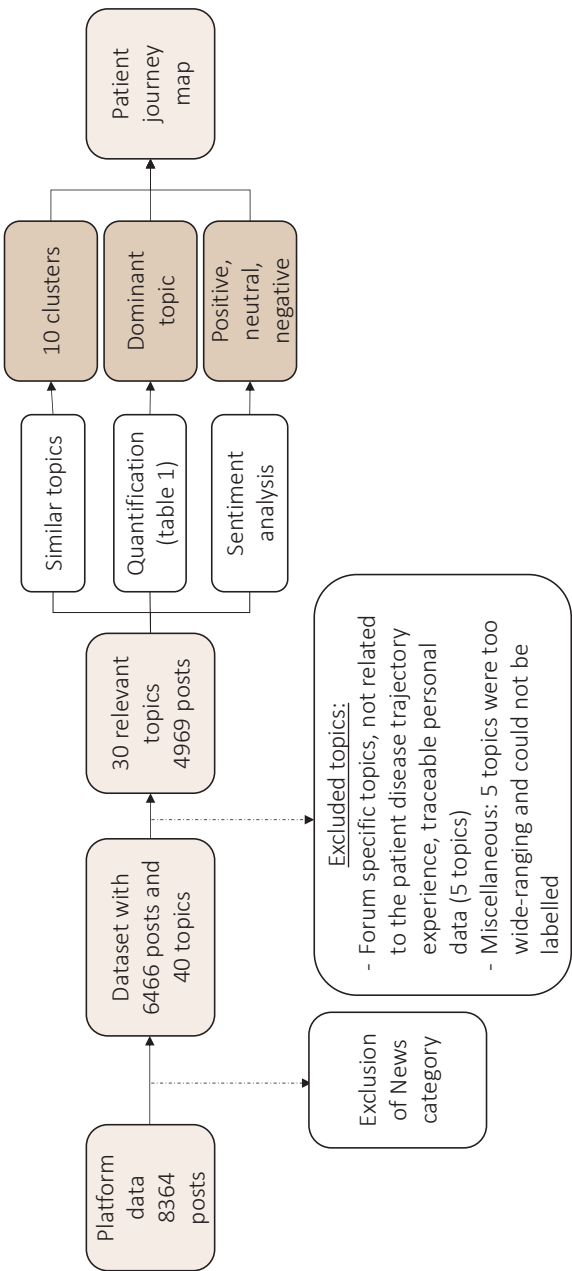


Figure 2. Study flowchart

Table 1 Results of the topic modeling and researchers' label of each topic

Clusters and topics	No. of posts	Percentage out of valid posts
1. Symptoms	1183	23.8%
1.1 Challenge and impact of small fiber neuropathy	192	
1.2 Describing unexplained symptoms	183	
1.3 Experiencing variation in symptoms per season	163	
1.4 Impact of sarcoidosis on eyes and vision	165	
1.5 Losing or gaining weight	178	
1.6 Sharing general experiences about symptoms	149	
1.7 Strategies to relieve symptoms	153	
2. Disease modifying medication	796	16.0%
2.1. Benefits and side effects of anti TNF-α inhibitors	220	
2.2. Benefits and side effects of immunosuppressive medication	203	
2.3. Differentiating between symptoms and side effects of medication	200	
2.4. Benefits and side effects of steroids	173	
3. Impact on daily life	568	11.4%
3.1. Balancing rest and activity to manage fatigue	187	
3.2. Benefits of sports and exercise	164	
3.3. Managing sleep and sleep disorders	148	
3.4. Living with sarcoidosis	69	
4. Other medication	498	10.0%
4.1 Weighing risk and benefits of vaccination	177	
4.2 Effect of different types of pain medication	174	
4.3 Effect of methylphenidate on fatigue	147	
5. Non-pharmacological interventions	418	8.4%
5.1. Effect of nutrition and diets on inflammation	146	
5.2. Sharing information about life-style intervention	138	
5.3. Strategies for maintaining physical and mental wellbeing	134	
6. Sarcoidosis and work	351	7.1%
6.1. Issues with work ability assessment	186	
6.2. Balancing between work and sarcoidosis	165	

Table 1 Continued

Clusters and topics	No. of posts	Percentage out of valid posts
7. Diagnosis and prognosis	346	7.0%
7.1. Challenges in diagnostic process	176	
7.2. Navigating in the complexity of diagnostic process	170	
8. Causes and mechanisms of disease	320	6.4%
8.1. Questioning about the cause and treatment	161	
8.2. Exploring impact of vitamin deficiencies on sarcoidosis	159	
9. Emotional support	317	6.4%
9.1. Looking for peer support	165	
9.2. Expressing empathy and understanding	152	
10. Alternative treatment	172	3.5%
10.1. Sharing experiences about alternative medicine	172	
Total	4969	100.0%

Patient journey map

To visualize patients' experiences with the current care pathway, we created a patient journey map based on the MLD analysis of the platform (**Figure 3**). Additionally, the map highlights the sentiment of the posts, represented by the color of each box. Most of the topics had a neutral or negative sentiment. The sentiment of the topics on symptoms, balancing sarcoidosis and work, and causes and mechanisms of the disease was mainly negative. Peer support, sports and exercise, balancing rest and activity to manage fatigue and sharing experiences about alternative medicine were alluded to with positive sentiment.

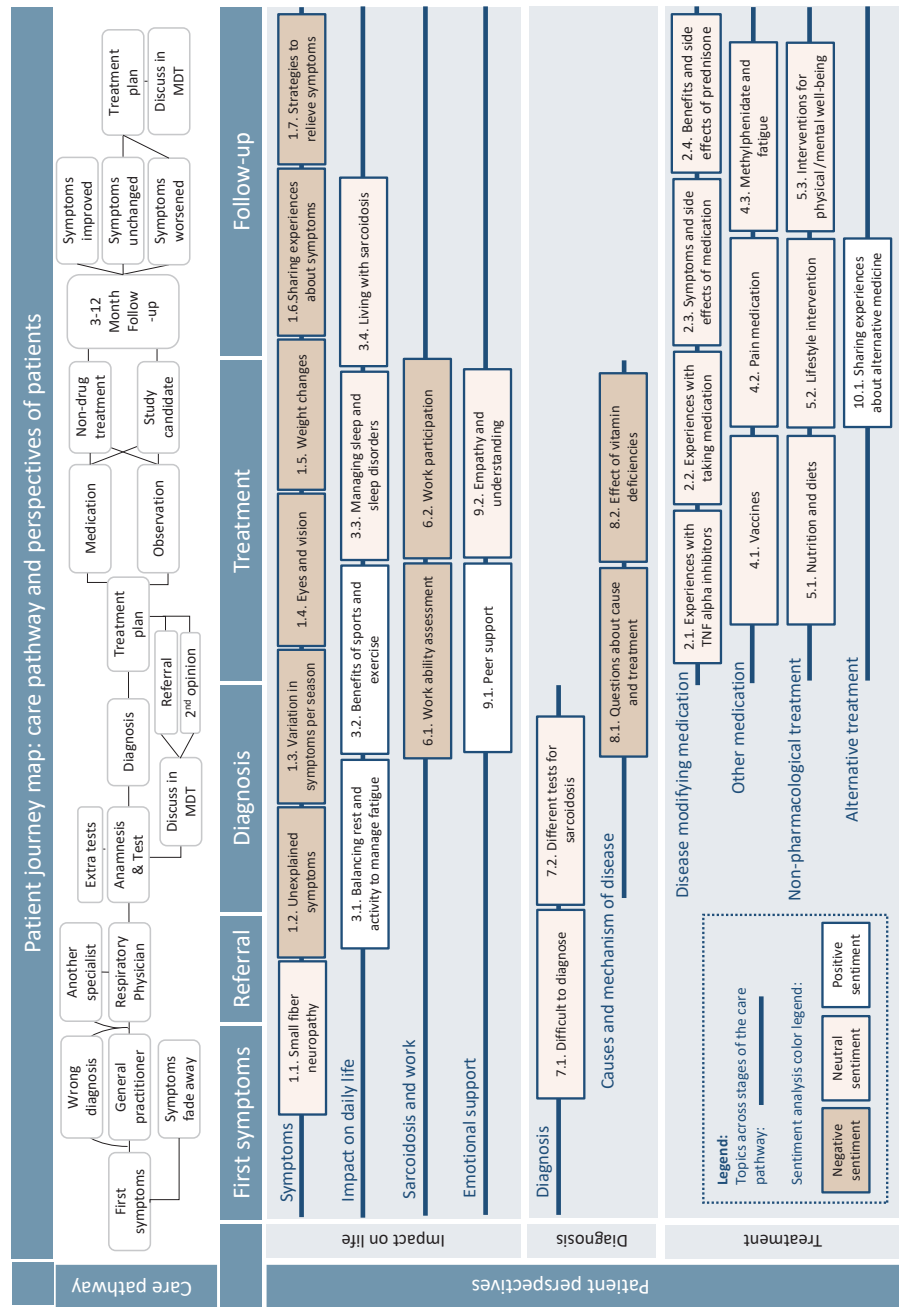


Figure 3. Patient journey map

Co-creation sessions and patient's feedback

The patient journey map was validated during co-creation sessions with clinicians, a nurse specialist, and a patient panel. Based on the discussion during the co-creation sessions the importance of providing patients comprehensive education about their disease was highlighted.

Patients

- 'Patients will always have questions regarding their illness'
- 'The patient journey map is very helpful for doctors so they can see what is important for patients'

Healthcare providers

- 'Probably we should do more about explaining the disease, but we only have 15 min'

Discussion

This is the first study to apply an MLD approach to analyze patient forum posts and develop a patient journey map derived from the narratives of patients with sarcoidosis. Using this approach, we were able to assess unsolicited patient needs and perceptions of patients with sarcoidosis, outside the scope of the hospital. The most frequently discussed topics focused on symptoms, disease-modifying medication and impact on daily life. Overall, patients consistently expressed a clear need for better disease education and a holistic management approach.

The MLD approach facilitates efficiently analyzing a large dataset such as in this study of online stories of patients. This enabled us to explore patient perspectives outside the scope of the hospital and include patient-driven and everyday-life data, in contrast to survey studies and questionnaires, which are often using predefined questionnaires that could lead to socially desirable answers and are often limited in sample size. MLD could potentially not only yield novel information on patient needs but could also be used to efficiently map changing patient perspectives and needs, for instance if novel management options would become available.

The current study revealed that most patient stories focused on symptoms and expressed a negative sentiment, highlighting a substantial symptom burden among patients with sarcoidosis. This mirrors findings of several studies that symptoms often have a significant impact on quality of life (2, 10, 11). Patients were uncertain whether symptoms were related to sarcoidosis or a side effect of medication. Also, non-organ related manifestations, such as fatigue and small fiber neuropathy were discussed. Disease modifying medication was the second-largest cluster and was also associated with a neutral sentiment. Patients were discussing benefits and side effects of disease modifying medication. Overall, many patients wanted more information about symptoms, available treatments, and their potential side effects. The lack of disease education is also reported in previous studies in round 41% patients (3, 12). Many patients access the internet to obtain information; however, this information is often insufficient (13).

Adequate information is a prerequisite for shared decision-making, which is strongly advocated for in the current guidelines (14). Nevertheless, in clinical practice shared decision making still strongly depends on the treating physician or specialist nurse. In the stakeholder meetings in our study, healthcare providers acknowledged that ideally, they would offer more comprehensive

disease education, however, time constraints make this challenging. Optimal ways and tools to provide tailored education and facilitate shared decision making deserve more attention in the sarcoidosis field. Digital solutions, such as online self-management tools and care programs (15, 16) hold promise to improve access to education and improve self-management and shared decision making. However, implementation and use of such tools may pose other challenges in turn (17).

In general, our findings align with scientific literature, which is reassuring that with a less labor-intensive method patient perspectives can be captured. Nevertheless, our method also identified some topics that are less frequently mentioned in surveys and interview, such as, an unmet need regarding counseling on diets and lifestyle interventions. In sarcoidosis, the prevalence and impact of malnutrition is currently unknown. Whereas inflammation can lead to weight loss, treatment with corticosteroids often leads to weight gain (18, 19). Assessing nutritional status and the effects of dietetic support in patients with sarcoidosis offers an opportunity to optimize patient-centered care and mitigate associated comorbidities. Furthermore, patients questioned how diet and vitamin deficiencies—particularly vitamin B12, D, and calcium—affect inflammation. However, no data currently exist on the role of nutrition in managing sarcoidosis. In other chronic inflammatory diseases, such as rheumatoid arthritis (RA), it has been suggested that diets, in particular Mediterranean diet, omega-3 fatty acids, could reduce inflammation and symptoms (20– 22). If this also holds potential for patients with sarcoidosis remains to be elucidated.

The impact of living with sarcoidosis on work-related aspects was also addressed by patients in our study. Patients discussed challenges with work ability assessments and shared their experiences of balancing work and the disease. This corresponds with findings of a previous Swedish study, in which patients with sarcoidosis experienced a reduction in workability, leading to a financial loss of 8%, which persisted up to five years after diagnosis (23). Another study demonstrated that 37% of the patients perceived a lack of attention during work-ability assessments and 38% disagreed with the assessment outcome (24).

A recent expert opinion statement recommended that work-ability assessment should be based on a patient-centered, holistic approach, which incorporates the personal experiences of living with sarcoidosis, and highlighted the need for additional guidance to reflect these patients' perspectives more accurately (25).

This study focused on collective patient experiences, rather than on individual trajectories, therefore information could not be analyzed chronologically for individual patient trajectories. Future research could employ dynamic topic modeling or temporal clustering, to further elucidate how patient experiences evolve over time. We particularly used TF-IDF combined with NMF for its interpretability, transparency, and computational efficiency, allowing for clear theme extraction from large datasets. While advanced techniques like transformer-based models (e.g., BERTopic) capture deeper semantic nuances and context, they come with trade-offs, such as reduced interpretability and increased computational demands. Future research could compare these advanced techniques to assess whether they better capture subtle semantics at the cost of interpretability. For sentiment analysis, we selected XLM-RoBERTa, an unsupervised multilingual transformer-based model, due to its training on diverse language datasets (including Dutch), which also provides strong cross-lingual capabilities. For future studies, we propose an opportunity to measure the model performance by generating pseudo-labeled data from a patient forum and to conduct additional fine-tuning of the model.

Our study also has several limitations. As this was an anonymized study of online patient stories, patient characteristics are lacking. Although patient journey mapping enables to analyzing a large-scale data set, there is a selection bias of patients who like to share their experiences online, this could depend on certain patients' characteristics, such as, educational level, or socioeconomic status, which in other fields have been associated with online access. We also encourage future studies to incorporate multi-source data, such as follow-up questionnaires, to validate the findings from the patient journey map. Furthermore, social media platforms are often nation specific, and the result of this study gives an overview of patients' experience in the Netherlands. In addition, the MLD technique is not always perfect in grouping posts in a medically and human logical way. For instance, posts mentioning blood were all grouped, whilst these contained stories about oxygen diffusion, iron deficiencies and hemoptysis. Human overreading categorized these groups as miscellaneous currently. Whereas the technique is not yet ready to use without critical human appraisal, one could envision that the MLD algorithm could improve when further trained with human feedback. Furthermore, the pre-specified number of 40 topics might have led to a loss of granularity on scarcely mentioned topics that could still be relevant. On the other hand, quantification of topics also allows prioritization when designing care pathways. Collaboration over the walls of our medical faculties with technical universities, AI scientists and implementation specialist will be needed to fully utilize and optimize the potential of techniques as MLD, sentiment analysis and care pathway design and implementation.

In conclusion, MLD is an innovative approach to analyze a vast collection of patients stories from their own narratives. MLD can provide a comprehensive overview of patients' perspective on health and care. Integrating these insights in future medical health care pathways for patients with sarcoidosis has the potential to improve patient-centered care and patient empowerment.

Acknowledgements

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Part IV

DISCUSSION

Chapter 13

GENERAL DISCUSSION



General discussion

The impact of sarcoidosis on patients' daily lives has been increasingly recognized in recent years. However, this recognition has not yet translated to proportionate attention, funding and research. Addressing this gap is essential to advance toward more evidence-based and personalized care. This thesis aims to contribute to improving treatment strategies and outcomes for patients with sarcoidosis. The first part of this thesis focused on improving pharmacological treatment and the second part on strategies to improve fatigue and quality of life. Below, I will place these findings in the context of current knowledge and explore their implications for future care and research.

Improving Pharmacological Treatment for Patients with Sarcoidosis

Since 1951, corticosteroids have been the cornerstone of treatment for pulmonary sarcoidosis (1). While they are effective in improving pulmonary function, radiographic findings and symptoms in the short-term, it remains unclear whether prednisone therapy slows down disease progression or prevents development of pulmonary fibrosis in the long-term (2, 3). Furthermore, its use is often accompanied by burdensome side effects and morbidity (3-6). The need for alternative, less toxic treatment options was already highlighted in the first official American Thoracic Society, European Respiratory Society and World Association of Sarcoidosis and Other Granulomatous Disorders (ATS/ERS/WASOG) statement in 1999(7). Although our understanding of disease mechanisms has markedly progressed over the last 20 years, this has not yet resulted in better evidence-based therapies (**Figure 1**). Subsequently, all the recommendations in the updated 2021 ERS clinical practice guideline were based on very low to low quality of evidence(8). Many of the research gaps highlighted in the 1999 guideline (who to treat, when to treat, how to treat, and how long to treat) remain largely unclarified in the 2021 update. In **chapter 3**, we compared the guidelines for sarcoidosis of the British Thoracic Society (BTS) and ERS guidelines, published within 1 year. Despite using the same evidence, there were slightly different recommendations, especially with regard to medication dosages. This highlights that sarcoidosis treatment is currently mainly based on common sense and is still in search of evidence.

First-line treatment

The ERS guideline makes a strong recommendation for corticosteroids as first-line treatment for patients with pulmonary involvement at risk of mortality or future morbidity (low quality of evidence)(8). The revised recommendation to initiate prednisone at 20 mg, rather than 40 mg, was based on evidence from a retrospective cohort study(9). Recently, a randomized controlled trial, the SARCORT trial, evaluated whether a high-dose of prednisone (40 mg per day) provided better outcomes compared to a low-dose prednisone (20 mg per day) in patients with sarcoidosis(6). The trial's combined primary endpoint included relapse rate (defined by clinical, physiological, and radiological parameters) and treatment failure after 18 months. The results showed that initiating treatment with 40 mg per day was not superior to 20 mg per day. While this landmark trial addressed a key question, it also revealed some methodological issues (10). In a complex disease like sarcoidosis, including a diverse patient population (patients with any manifestation requiring treatment), may reduce accuracy of findings, as patients with different manifestations and

disease severity might respond differently to treatment. Furthermore, the combined endpoint (relapse and treatment failure), which grouped patients with an initial response to treatment together with patients who were non-responsive to treatment, complicates the interpretation and generalizability of the results.

An important outcome of the SARCORT trial was that adverse events were comparable between the high- and low-dose prednisone group, highlighting the need for alternative treatments with less toxicity. Methotrexate is the recommended second-line treatment, and early initiation of methotrexate is advised, to reduce toxicity from long-term corticosteroids use (8, 11, 12). In **chapter 4**, we assessed patient experiences with prednisone and methotrexate in a cross-sectional survey study among patients who used prednisone or methotrexate (present or former). This survey study suggested that methotrexate may be associated with fewer and less burdensome side effects compared to prednisone. This highlighted the need for a prospective study and led to the design of the PREDMETH trial, a randomized controlled non-inferiority trial, in which we investigated the efficacy of methotrexate compared with prednisone as first-line treatment for pulmonary sarcoidosis (**chapter 6**). We hypothesized that methotrexate would be as effective as prednisone and would have fewer side effects. Secondary endpoints included the effect of both medications on quality of life and patient-reported outcomes measures (PROMs). Additionally, a home monitoring program was implemented to assess weekly symptoms scores, patient-reported side effects and home spirometry. These data allow to evaluate the time to treatment effect in more detail. Another important exploratory endpoint focuses on the analyses of blood samples, which may lead to the discovery of new biomarkers for better predicting response to therapy.

The PREDMETH study opened for inclusion in February 2020; however, due to the onset of the COVID-19 pandemic in March 2020, we decided to temporarily pause inclusion. We reviewed the literature to assess whether patients with sarcoidosis had an increased susceptibility to COVID-19 or an increased risk of adverse events (**chapter 5**). The severity of pulmonary function impairment was associated with an increased risk of severe COVID-19 complications(13, 14). Although evidence was limited and somewhat conflicting, the use of corticosteroids and methotrexate did not seem to increase the risk of severe COVID-19 complications(13, 15-17). This prompted us to resume inclusion of the PREDMETH trial, as it was conceivable that immunosuppressive treatment, aimed to reduce inflammation and improve pulmonary function, could reduce the risk of adverse outcomes of COVID-19 in patients with pulmonary sarcoidosis.

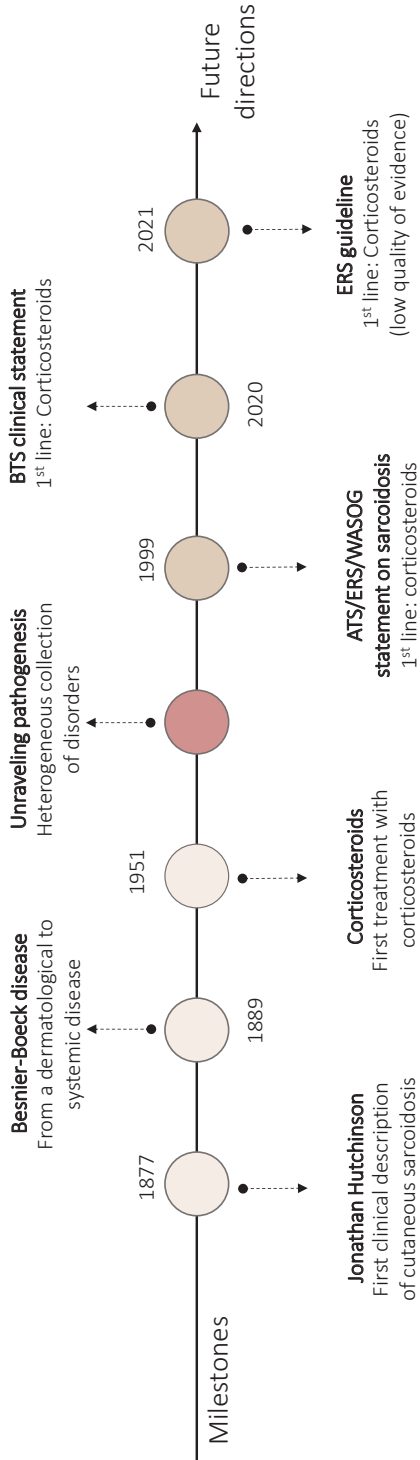


Figure 1. Historical perspectives on the treatment of sarcoidosis

Chapter 7 in this thesis outlines the findings of the PREDMETH trial, showing that methotrexate is non-inferior to prednisone as first-line treatment for pulmonary sarcoidosis as assessed by change in FVC after 24 weeks of treatment. The total number of adverse events was similar in both groups, however, at 24 weeks fewer adverse events were ongoing in the methotrexate group. In line with expectations, the reported adverse events were clearly different. For the prednisone group weight gain (mean +5.0 kg $\pm$ 5.1), insomnia and increased appetite were the most common side effects. For methotrexate nausea, fatigue and liver function abnormalities were most common. This trial provides the first high-quality evidence comparing first-line treatment options for pulmonary sarcoidosis and demonstrates that methotrexate can be considered as an alternative for prednisone for patients with pulmonary sarcoidosis. The differences in side effect profiles offer valuable information for shared decision-making and personalized treatment.

As expected, the time to efficacy differed between prednisone and methotrexate. Prednisone led to a rapid increase in FVC during the first 4 weeks, while the methotrexate group had a slower onset of efficacy. Interestingly, an improvement in lung symptom scores could already be seen after 4 weeks of treatment in both groups. This is in line with previous findings with corticosteroid treatment(18). In the prednisone group, the rapid increase in FVC during the first 4 weeks was followed by a trend of decrease after 16 weeks, with a similar trend for DLCO observed after one month. Similar observations were made for the PROMs and soluble interleukin-2 receptor (sIL-2R). A previous prospective study in newly treated patients with pulmonary sarcoidosis also showed a decreasing trend in DLCO after one month of treatment with prednisone(5). It is plausible that the subtle decrease in pulmonary function, PROMs and sIL-2R is related to an increase in inflammation during prednisone tapering. This hypothesis is further supported by data from previous trials. In the previously mentioned SARCORT trial, prednisone was discontinued after just 6 months of treatment, which may have contributed to the observed relapse rate of 45% within 12-18 months(6). In contrast, another study, reported a lower relapse rate of 14% when treatment was continued for at least one year(19). These observations support the notion that long-term treatment of sarcoidosis is likely needed to adequately suppress granulomatous inflammation and potentially reduces the risk of relapse after discontinuation of therapy.

In the PREDMETH trial, we also implemented a home monitoring program, in which patients performed weekly home spirometry and reported symptoms and side effects. Data are expected soon and will enable a more granular

assessment of time to major pulmonary improvement and reaching an effect plateau. As previously mentioned, the primary results of the PREDMETH trial were in line with what we hypothesized prior to the study: that methotrexate was non-inferior to prednisone after 24 weeks of treatment, however with a slower onset of efficacy. Previous studies demonstrated that time to major pulmonary improvement with prednisone occurred 2-3 weeks after treatment initiation(5, 18). However, the time to response when using methotrexate for pulmonary sarcoidosis remains unknown. There has been considerable debate about whether a slower onset of action is clinically acceptable for patients. As mentioned earlier some symptoms scores in the methotrexate group improved already after 4 weeks of treatment, suggesting that its effect on symptoms may begin earlier than previously assumed.

Furthermore, home monitoring has the potential to give better insights into the disease course for both patients and healthcare professionals and to personalize treatment(20). In the PREDMETH trial, healthcare providers received alerts when symptoms worsened, home spirometry declined, or patients experienced burdensome adverse events. This allowed for timely adjustment of medication when needed. In regular care, however, medication adjustments are typically made during hospital visits. I believe that home monitoring in patients with sarcoidosis could be a valuable tool to assess safety and tolerability, and to tailor the tapering of immunosuppressive treatment for individual patients. While studies assessing home monitoring in sarcoidosis are scarce, in other chronic respiratory diseases, more evidence is available that home monitoring and home spirometry are feasible, reliable and can provide guidance in optimizing and personalizing treatment for patients (21-23).

An ongoing randomized controlled trial, the DURASARC trial, investigates the efficacy of a 6-month versus 12-month prednisone regime for pulmonary sarcoidosis (NCT06654934). However, based on current knowledge, I believe that future trials should focus more on investigating alternative less toxic treatments or combination therapies rather than optimizing prednisone monotherapy. Data in cardiac sarcoidosis suggests better outcomes when prednisone and methotrexate are combined (24). In line with this, an ongoing randomized controlled trial is investigating the efficacy of low dose prednisone and methotrexate compared to standard dose prednisone in cardiac sarcoidosis(25). The authors hypothesize that this combination of low-dose prednisone and methotrexate will be non-inferior compared to standard-dose of prednisone, with fewer side effects and better quality of life.

I expect that the results of the PREDMETH study will pave the way for methotrexate as alternative first-line treatment for pulmonary sarcoidosis. The differences in adverse event profiles offer valuable information for shared decision-making between patients and doctors when selecting the most appropriate treatment for each individual. Ultimately, the optimal treatment for an individual patient requires balancing symptom control and risk of possible side effects. Some patients prioritize quick treatment effects and are less concerned about side effects, while others may be willing to wait longer for treatment effects to avoid steroid toxicity. Looking ahead, we hope to develop a decision aid tool that will assist both doctors and patients in navigating these choices, ensuring that treatment plans are tailored to meet each patient's unique needs and preferences.

In the PREDMETH trial, we also collected blood samples with several aims: validating an existing biomarker (sIL-2R) for treatment response, identifying new biomarkers through in-depth immune phenotyping, and evaluating their potential for monitoring and guiding treatment. In a previous smaller cohort, we demonstrated that increased proportions of circulating PD-1⁺CD4⁺ memory cells and PD-1⁺ regulatory T- cells were associated with a good response to treatment, defined as $\geq 10\%$ FVC in 12 months (26, 27). These findings suggest that T-cell phenotyping prior to treatment initiation may serve as a useful biomarker to predict treatment response. The data of the PREDMETH trial enables further validation of these findings. Furthermore, it is hypothesized that the variation in response to treatment may be influenced by corticosteroid resistance, which is mediated by low expression of glucocorticoid receptor and high expression of multidrug resistance-1 (28-30). Also, for methotrexate, there is an individual variation in response to treatment, which might be related to differences in metabolism. Methotrexate is an antimetabolite and folate antagonist and requires intracellular metabolism before it becomes pharmacologically active. It is converted by the enzyme folylpolyglutamate synthase (FPGS) by addition of glutamate residues, resulting in the formation of methotrexate polyglutamate (MTXPG) concentrations, which accumulate in cells and lead to anti-inflammatory effects. A previous retrospective study suggested a correlation between MTXPG concentrations and response to treatment in patients with sarcoidosis (31). Also in other inflammatory diseases, associations between MTXPG concentrations and disease activity were found (32-35). With the data of the PREDMETH trial, this relation will be further evaluated. These findings may contribute to the improvement of personalized treatment strategies for patients with sarcoidosis, potentially advancing our ability to tailor therapies to individual patient profiles.

Second-, third - and fourth-line treatment options

Current treatment recommendations follow a step-up approach (8, 36). If inflammation is not being adequately suppressed, escalation to another immunosuppressive treatment becomes necessary. Second-line treatment involves immunosuppressive agents, such as methotrexate, azathioprine, leflunomide, mycophenolate mofetil or hydroxychloroquine. Third-line treatment consists of biologicals, such as infliximab and adalimumab (TNF-alpha inhibitors) and fourth-line treatment includes a JAK-inhibitor or rituximab. Evidence supporting second-, third- and fourth-line treatment options is scarce, and more research is clearly needed. Whether a step-up approach is the optimal strategy or if early initiation of biological treatment in patients with severe disease leads to better outcomes remains to be elucidated (37).

Many studies evaluated third- and fourth line treatment options for patients with sarcoidosis. However, this poses some challenges as these studies are conducted in a patient population with more advanced and complex disease profiles, making it difficult to predict disease behaviour and choose the optimal endpoints (27, 38-42). Recently we extended the follow-up duration of the PREDMETH trial to be able to gain more knowledge about long-term disease behaviour of sarcoidosis. The PREDMETH trial could also provide important information in the ongoing debate about the optimal endpoint(s) to assess treatment response in pulmonary sarcoidosis. Currently, the most frequently used measure in pulmonary sarcoidosis is the change in FVC, however, the minimal clinical important difference (MCID) of FVC is currently unknown.

Treatment of fibrotic sarcoidosis

Around 5-20% of patients with pulmonary sarcoidosis develop fibrosis (43). The transition from inflammation to fibrosis in sarcoidosis is not well understood. Recent radiological and histological studies suggest that persistent inflammation could play an important role (44-50). Additionally, some studies have identified certain genetic profiles that may increase the risk of fibrosis, leading to the hypothesis that fibrotic sarcoidosis could be a distinct entity from its onset (51). Hopefully, the long-term data of the PREDMETH trial will provide new insights into risk factors for the development of fibrosis.

Until recently, immunosuppressive treatment was the only pharmacological treatment option for fibrotic sarcoidosis. More options became available after the publication of the INBUILD trial in 2019 (52). This randomized controlled trial, assessed the efficacy of nintedanib (a tyrosine kinase inhibitor) in 633 patients with

progressive fibrosing disease other than idiopathic pulmonary fibrosis (IPF). The primary endpoint was FVC decline at 52 weeks. Results showed that nintedanib slowed the decline of lung function compared to placebo over one year (81 ml per year vs. 188 ml per year). However, only 12 patients with sarcoidosis were included in this trial, with 4 patients receiving nintedanib and 8 patients receiving placebo, making it difficult to draw conclusions specific to sarcoidosis (53). A pilot study investigating the efficacy of pirfenidone in patients with fibrotic sarcoidosis was terminated prematurely due to the COVID-19 pandemic. Although no difference in efficacy was observed between the pirfenidone (n=11) and placebo group (n=5), the study was underpowered, and no definite conclusions can be drawn (54).

Due to the lack of evidence-based treatment strategies for patients with fibrotic sarcoidosis, treatment decisions should be guided by a multidisciplinary meeting. While fibrosis is often considered irreversible, ongoing active inflammation seems to play an important role in patients with fibrotic sarcoidosis (45-47, 55). Below I propose a stepwise approach for the management of fibrotic sarcoidosis (**Figure 2**). The first step is to assess if there are signs of active inflammation and optimize anti-inflammatory treatment according to the ERS clinical practice guidelines on treatment of sarcoidosis. Positron Emission Tomography – Computed Tomography (PET-CT) seems to be currently best available method in detecting inflammation, but also the most expensive (56, 57). A retrospective study showed that 22 out of 26 patients with fibrosis also had positive Fluorodeoxyglucose (FDG) uptake in fibrotic lesions including honeycombing (47). Although no threshold value is available to differentiate between active inflammation and fibrosis, some cohort studies showed that increased FDG uptake is associated with response to anti-inflammatory treatment in fibrotic sarcoidosis (55). sIL-2R can also be used to assess inflammation, but it is less sensitive than PET-CT, and in some patients, inflammation cannot be well detected with sIL-2R (58). Hopefully, new biomarker discoveries in the near future, such as exhaled breath analyses and blood biomarkers, will lead to improved diagnostic assessment of inflammation (59, 60). As a second step, antifibrotic treatment should be considered on a case-by-case basis in patients with progressive fibrosis, especially in patients with a usual interstitial pneumonia (UIP) pattern (61). A retrospective study showed that patients with a UIP pattern deteriorated faster and had a survival time similar to IPF patients, compared to patients with a non-UIP fibrotic pattern (61). Further, as patients with fibrotic sarcoidosis are at risk for infection and vascular complications, these should be assessed and adequately treated. Supportive measures like education, psychological support, rehabilitation, supplemental oxygen and palliative care programs have the potential to reduce symptoms and improve quality of life and

should be considered in all patients. Furthermore, in patients with progressive disease despite adequate treatment lung transplantation should be considered as it can improve quality of life (QoL) and prolong survival.

Challenges with endpoints in sarcoidosis clinical trials

As mentioned earlier, the heterogeneous nature of sarcoidosis and unpredictable disease course complicates study design, in terms of selecting patients and choosing clinical endpoints. This variability has led to a wide range of clinical outcomes used in clinical studies, making the comparison of results challenging, and potentially overlooking outcomes most important to patients (**Figure 3**). The importance of defining a core outcome set to standardize and guide clinical trial design was first discussed during the WASOG meeting in 2011, resulting in task force recommendations for several endpoints for different manifestations (62).

Since then, several studies have evaluated a clinical outcome set for patients with sarcoidosis. The first study, conducted by Kampstra et al., developed a core outcome set based on input from an expert panel, but did not include patient perspectives (63). Subsequently, the sarcoidosis outcome task force (SCOUT) developed a core outcome set that included opinions from patients, researchers and physicians (64, 65). However, despite these efforts, no standardized core outcome set (COS) has been widely implemented across clinical trials to date.

Recently, a systematic review evaluated the standardization of clinical trials conducted after the publication of the WASOG statement in 2012 and showed that most recent trials did not fully meet the recommendations, although they defined clear primary endpoints and incorporated QoL as outcome (66). This underscores the necessity to revise clinical trial guidelines in light of emerging evidence from novel studies. For pulmonary involvement the task force defined a relevant change as either a $\geq 15\%$ change in FVC alone or a 5-15% change in FVC when combined with serial chest radiographic evaluations (assessed as better, worse or unchanged). Whether this recommendation is realistic or specific enough can be debated. Chest radiographic evaluations are often not sensitive enough to detect subtle changes and do not correlate well with pulmonary function (67, 68). Indeed, a recent study demonstrated that HRCT provide additional information compared to standard chest radiography, which are more closely associated with pulmonary function impairment (69). Future evaluation is needed to define the role of HRCT in monitoring patients with pulmonary sarcoidosis. Furthermore, the mean FVC change was less than 15% in most studies involving treatment naïve patients with pulmonary sarcoidosis (**Table 1**).

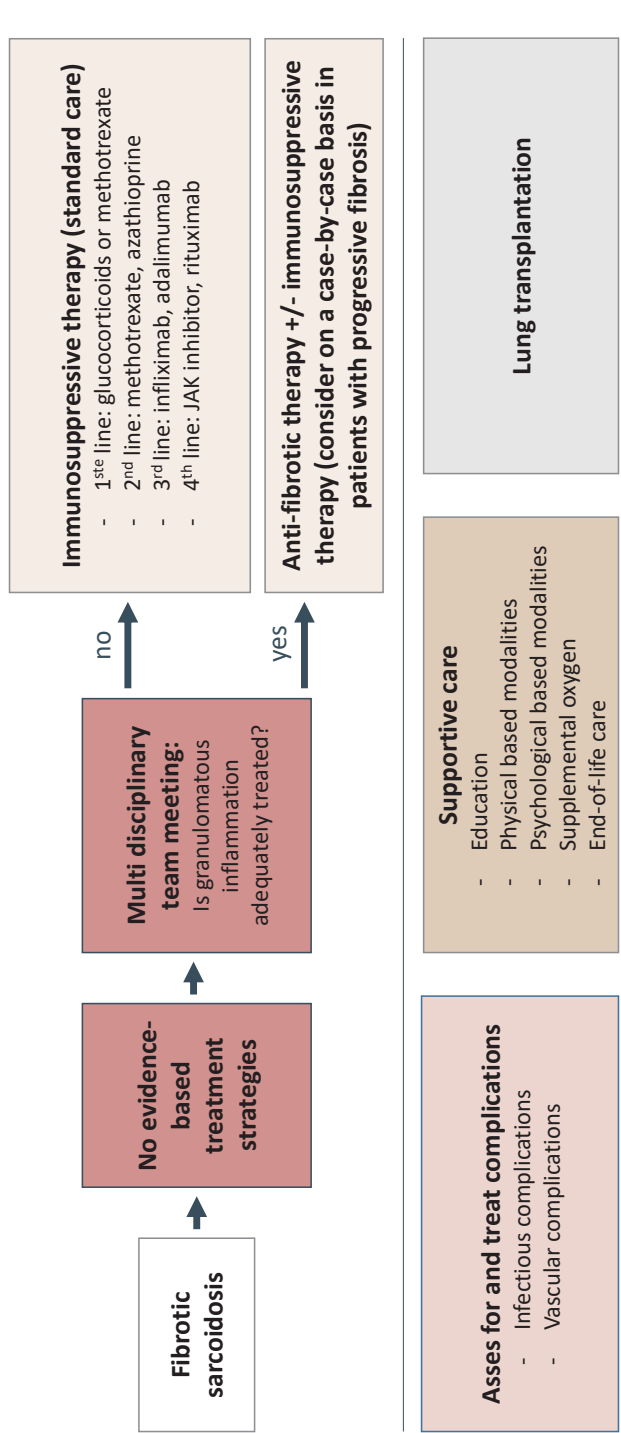


Figure 2. Approach for the management of fibrotic sarcoidosis. Due to the lack of evidence-based strategies patients should be discussed in a multidisciplinary team meeting. * The suggested approach based on the data from the PREDMETH trial has not yet been incorporated into clinical treatment guidelines.

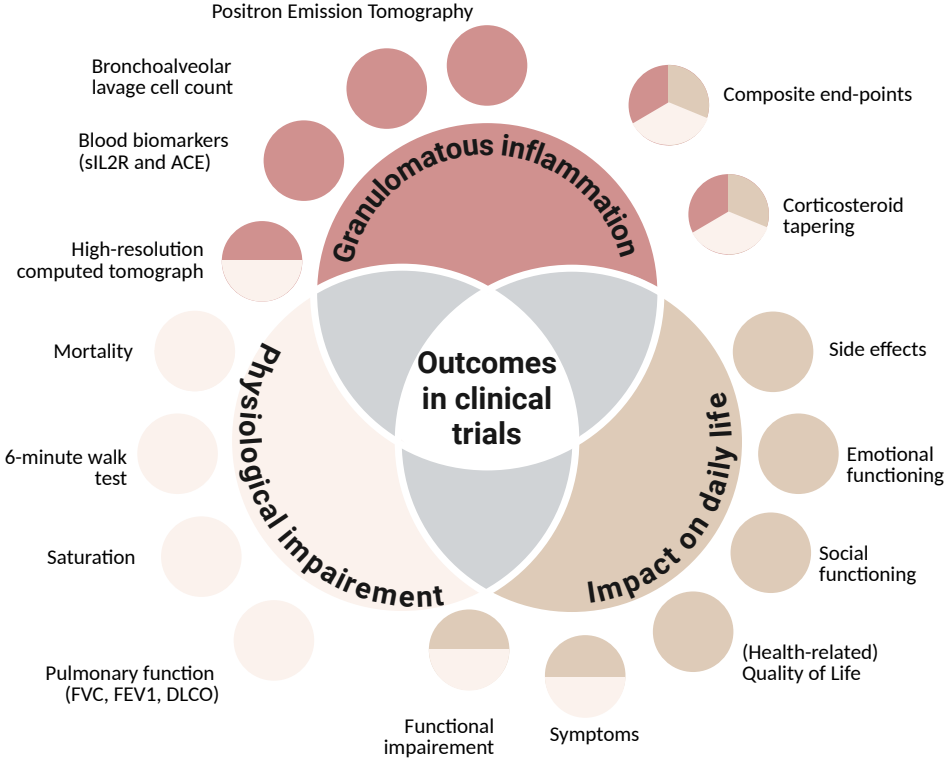


Figure 3. Treatment outcomes for pulmonary sarcoidosis. The evaluation of new treatments should consider three key components of the disease; I) granulomatous inflammation which; II) physiological impairment; III) the impact of sarcoidosis on daily life of patients.

The PREDMETH trial demonstrated that $\geq 5\%$ FVC increase was observed in 53% of patients; 42% had stable FVC (between -5 and 5%), and 6% had a $\geq 5\%$ decline. Furthermore, a clinically meaningful improvement in Kings Sarcoidosis Questionnaire Lung score (≥ 4 points) was seen in 58% of patients, while 31% had no meaningful changes, and 11% had a decline (≤ 4 points). A combined endpoint defined as either a $\geq 5\%$ increase in FVC and/or a ≥ 4 -point improvement in King's Sarcoidosis Questionnaire (KSQ) Lung Score was met by 73% of patients (**Figure 4**). Interestingly, 22% of patients experienced clinically meaningful improvements in symptoms without substantial changes in FVC. On the other hand, 14% of patients had a $\geq 5\%$ increase in FVC without improvement in symptoms. These findings illustrate the challenge of identifying appropriate

endpoints in pulmonary sarcoidosis and highlight the need to incorporate patient-reported outcomes to more comprehensively assess treatment response in pulmonary sarcoidosis. We are currently using the PREDMETH data to assess the MCID for FVC.

Table 1: Studies reporting change in FVC in treatment-naïve patients

Author	Design	Treatment	N	Intervention Change in FVC% pred.	Comparator Change in FVC% pred.
Gibson 1996	RCT 12 months	• Prednisone • Selective treatment*	58	Prednisone 10.4%	Selective treatment 2.6%
Broos 2015	Prospective 3 months	• Prednisone	21	15.1%	
Broos 2018	Retrospective 12 months	• Prednisone 40mg • Prednisone 20mg	54	9.6% no difference between arms	
Dhooria 2022	RCT 6 months	• Prednisone 40mg • Prednisone 20mg	86	Prednisone 40mg: 6.3%	Prednisone 20mg: 5.2%
Kahlmann 2024	RCT 6 months	• Prednisone • Methotrexate	137	Prednisone 6.7%	Methotrexate 6.1%

*Selective treatment: in this group, prednisone treatment was restricted for specific indication based on worsening symptoms or decline in pulmonary function; otherwise patients remained under observation.

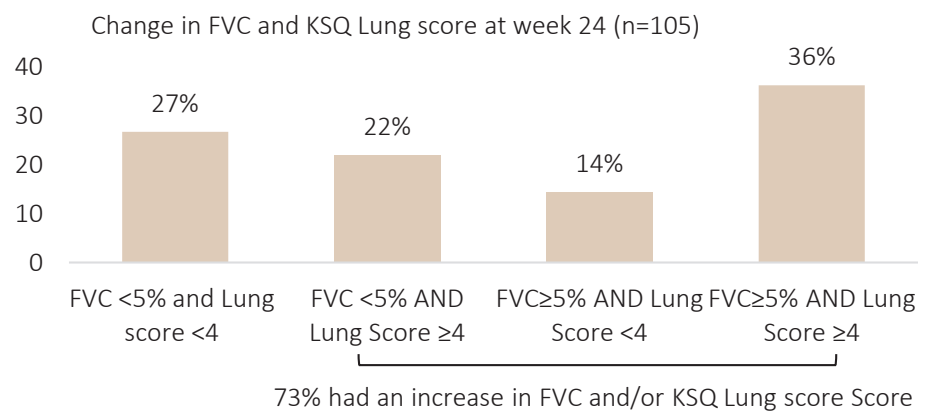


Figure 4. Exploratory data of the PREDMETH trial: combined endpoints of change in FVC and KSQ Lung score (presented at WASOG conference 2025, Ottawa, Canada)

Patient-reported outcome measures (PROMs) are increasingly recognized as critical endpoints in clinical trials (70). However, currently there is a considerable variability in the PROMs used in clinical trials, which complicates the comparability of results (70). Reliable and validated PROMs are needed to accurately evaluate the impact of treatment on patient’s wellbeing. The integration of standardized PROMs in clinical trials has the potential to generate valuable data that can better validate clinically meaningful changes.

The KSQ is a validated questionnaire to assess health status in patients with sarcoidosis and currently one of the most frequently used PROMs to assess health status in patients with sarcoidosis (71).The current MCID was determined by distribution and anchor-based analysis in a non-interventional study (72, 73).The PREDMETH trial provides the first opportunity to evaluate the responsiveness of the KSQ in an intervention trial. Although the KSQ is the best validated questionnaire for sarcoidosis, it is relatively long and time-consuming for patients, particularly for routine clinical practice. There is a need for shorter, user-friendly questionnaires that can detect subjective changes in patients’ symptoms and are easy to use and interpret. Recently, for patients with IPF, the use of visual analogue scales was found to be valid and reliable for the assessment of symptoms over time(74, 75). Whether this also applies for sarcoidosis will be evaluated by assessing the correlation between the weekly VAS scores and PROMs.

Outstanding questions for future research

This thesis provides further evidence on the optimal treatment for patients with sarcoidosis. Additional research is needed to further refine classification and treatment strategies. Below some important outstanding research questions:

- Which patients are in need of immunosuppressive treatment?
- Can we better predict disease course and response to treatment?
- Is fibrotic sarcoidosis a different phenotype from the beginning?
- Does early aggressive immunosuppressive therapy prevent formation of fibrosis?
- What is the role of antifibrotic therapy in sarcoidosis?
- How can we optimize outcome measures to assess treatment response for different therapeutic interventions?

Improving Quality of Life for Patients with Sarcoidosis

Over the last decade, the healthcare landscape has been evolving and transforming from physician-directed to patient-centered care. Patient-centred care focuses on the individual needs, preferences and values of patients in all aspects of their care. This approach actively engages patients in the decision-making process and requires a close collaboration between the patient and healthcare professionals. Especially in sarcoidosis, a chronic disease with an unpredictable course that significantly affects patients' quality of life, patient-centred care is crucial. Providing patient-centered care requires a broad understanding of patients' needs and perceptions, including the impact of living with sarcoidosis on their daily lives. Several studies identified gaps in the care for patients with sarcoidosis. In addition to treatment optimization, key unmet needs in sarcoidosis include a comprehensive and holistic approach to care, management of non-organ manifestations, and patient education.

A comprehensive and holistic approach to care

Sarcoidosis can affect nearly any organ, leading to a highly variable clinical presentation. In **Chapter 2**, we described the ABCDE-model, which can be used as a guide for a comprehensive approach to systematically assess health status and the impact of sarcoidosis on daily life. Whether the implementation of this model is feasible in clinical practice and could effectively improve outcomes remains yet unclear. Ideally, health-care providers would have more time to explore the impact of sarcoidosis on quality of life (**Chapter 12**). However, with consultation times typically limited to 10-15 minutes, it can be challenging to assess all aspects of care. A possible approach to address this could be a short pre-consultation online questionnaire, where patients report symptoms and their impact on daily life using visual analogue scales (VAS), facilitating more efficient and focused discussions during consultations. In the PREDMETH trial (**Chapter 5 and 6**), patients reported side effects and symptoms in the online home monitoring app on a weekly basis. Patients were generally positive about the online home monitoring program. They found it easy to use and not burdensome. Patients valued healthcare providers' direct access to their data and reported home monitoring enhanced their engagement in disease management. I believe that integrating online home monitoring in research and clinical care holds promise to improve patient-centered care and should be further investigated (20). Currently, we are developing a digital self-management application for people with sarcoidosis to improve disease education and provide information about lifestyle management.

Non-organ-specific manifestations of sarcoidosis

Some of the most common symptoms of sarcoidosis are not visible and are therefore easily overlooked. These invisible symptoms are often referred to as non-organ-specific manifestations and include fatigue, stress, anxiety, depression, cognitive impairment. These symptoms often interact with each other, leading to a downward vicious circle, negatively affecting patients' overall wellbeing and quality of life (76-78). As patients often look completely healthy, they may experience misunderstanding about the impact of their symptoms, and their ability to fully participate in society, including the workplace (79, 80).

Although broadly acknowledged that the management of non-organ manifestations should receive more attention, research into new treatment options is scarce (81). In **chapter 8**, we discussed approaches to assess and manage these non-organ-specific manifestations and provide future directions for research.

Fatigue is the most common symptom of sarcoidosis and often reported as the most burdensome (77, 79). Management of fatigue remains a great challenge for both patients and physicians. The etiology of fatigue is complex, involving multiple factors (physical, psychological and social), so a one-size fits all approach to its management or treatment is not feasible. Given the scarcity of evidence-based treatment strategies, a personalized, comprehensive, multidisciplinary approach aimed for personalized approach seems to be most suitable. In **Chapter 9**, we proposed a decision-making flow-chart to guide assessment and management of fatigue in patients with interstitial lung diseases. We also highlighted that better treatment strategies for fatigue represent one of the key unmet needs in the care for patients with sarcoidosis.

Fatigue is not specific to sarcoidosis, but common in many chronic diseases (82). Previous studies, mainly focusing on fatigue in cancer-survivors, showed promising results of the effect of cognitive therapy on fatigue (83). Together with the Dutch sarcoidosis patient organization (sarcoidose.nl) we conceived the idea to evaluate the potential benefits of cognitive therapy in patients with sarcoidosis. This has led to the design of the TIRED trial, a randomized controlled trial, in which we investigated the effect of online mindfulness-based cognitive therapy (eMBCT) on fatigue in patients with sarcoidosis. In line with our hypothesis, this study showed that eMBCT led to a significant and clinically relevant improvement of fatigue, symptoms of anxiety, depression, and mindfulness in patients with sarcoidosis (**Chapter 10**). Interestingly, a non-significant improvement in fatigue

scores was observed in the control group. Patients in the control group had a screening visit at the hospital and subsequently a screening visit with a psychologist of the Helen Dowling Institute. We believe that attention by health care professionals could have led to increasing insights into fatigue and better self-management. This observation also provides valuable insights for future research. Since eMBCT is a quite comprehensive program, one could envision that patients might also benefit from a less intensive program.

Three months after completing the eMBCT program the improvement in fatigue, anxiety, depression and mindfulness persisted. We believe that having access to the educational information and mindfulness exercises after completing the program could be beneficial in retaining the ability to cope with fatigue. We did not assess outcomes after six months, though, based on experiences in clinical practice is likely that a refresher course could be beneficial for patients. Some of the patients that participated in the Tired Trial had a refresher course and reported positive effects.

We hypothesize that besides patients with sarcoidosis, patients with other chronic respiratory disorders suffering from fatigue and other psychological symptoms might also benefit from eMBCT. Indeed, a recently published study also showed that a digital cognitive behavioural therapy improved anxiety in patients with pulmonary fibrosis (84). The advantage of these online programs is that they can easily be implemented in clinical practice and will lower the burden on the health system.

To provide better individually targeted treatment, research is needed into factors that predict treatment success, both for physical and psychological-based interventions. Furthermore, there is a need for an objective biomarker to measure fatigue and psychological wellbeing in sarcoidosis. Hair glucocorticoids (HairGC) levels have been associated with chronic stress and wellbeing in other conditions (85-87). Therefore, we conducted an exploratory analysis of the relation between HairGC levels, fatigue, and psychological symptoms in patients with sarcoidosis who participated in the Tired Trial (presented at ERS conference 2025, Amsterdam, The Netherlands). Patients who were currently using corticosteroids were excluded from analysis, as corticosteroid treatment significantly reduces HairGC levels. However, previous corticosteroid use or other immunosuppressive treatment were not excluded. At baseline, we did not find an association between fatigue, psychological symptoms, and hairGC levels (adjusted for gender, age and body mass index (BMI)). This contrasts the findings

of van Manen et al., who reported moderate associations between hairGC levels and psychological stress, though not with fatigue (87). There could be several explanations. First, differences in study population may play a role, van Manen et al. only included patient without inhaled or systemic corticosteroid use in the last year, whereas in our study, former corticosteroid users were included. Second, growing evidence suggests that factors such as BMI, waist circumference, and metabolic syndrome are associated with HairGC levels (88, 89). Van Manen et al. did not adjust for these variables, whereas in our analysis we adjusted for BMI. In our cohort, we also assessed longitudinal changes in HairGc a did not find a difference between responders and non-responders in the intervention arm (patients who underwent eMBCT). Thus, while cognitive therapy reduced fatigue and psychological symptoms, this was not reflected in changes in hairGC levels. However, the number of participants were small, so the results could have been underpowered to detect a significant difference.

Patient education

Comprehensive disease information and patient education are essential for effective shared decision-making, implementation of self-management strategies and medication adherence. However, many patients with sarcoidosis report insufficient access to disease-related information (79, 90-92). In **Chapter 12**, we employed an innovative, data-driven approach to identify the unmet needs and care gaps of patients with sarcoidosis. Based on this analysis we developed a patient journey map that outlined key topics based on home- and hospital care experiences. Patients most often spoke about their symptoms, disease-modifying medications, and how living with sarcoidosis affected their daily routines. Patients consistently highlighted the need for better disease education and a more holistic, comprehensive approach to care. While this promising approach allows assessment of a large collection of data on patient-reported experiences and holds potential for rapid reassessment of patient perspectives in light of new developments, it still requires further validation to confirm its broader applicability.

Although healthcare providers recognize the importance of providing comprehensive information, time limitations and rising healthcare demands make this challenging. Moreover, even when comprehensive disease education is provided, it is important to realize that 40-80% of the medical information is instantly forgotten and about half of the information is incorrectly remembered (93). Previous studies in other diseases showed that information is better retained when verbal information is complemented with written educational

information (94). Furthermore, combining written information with visuals could further improve recall for medical information, especially in patients with low literacy (95). In sarcoidosis, approaches to improve adequate patient education remain under investigated. Promising approaches that have shown to effectively improve patient education in other chronic diseases include the use of visual aids, implementation of question prompt sheet (QPS), conversation aids and personalized teaching/action plans (96). The digitalization of healthcare offers new opportunities, with innovative approaches holding potential to improve patient education and management. Online self-management interventions, such as educational information, online exercise and lifestyle interventions, have demonstrated positive effects on quality of life and self-efficacy in patients with other chronic diseases (97-99).

Outstanding research questions

This part of the discussion focused on optimizing patient centred care and improving quality of life. We gathered valuable insights on unmet needs from a patient perspective and provided new evidence for the treatment of fatigue with online mindfulness-based cognitive therapy. However, more research is needed to enhance the quality of life for people living with sarcoidosis. Outstanding questions include:

- How can patient-relevant outcomes be assessed using brief, validated questionnaires that are both reliable and minimally burdensome (time consuming)?
- How can the management of non-organ manifestations, such as fatigue, small fiber neuropathy, and pain be improved?
- Which patients do benefit most from physical activity programs and which patients benefit more from psychological support?
- Are there common mechanisms of fatigue across chronic (post) inflammatory disease?

CONCLUSION

To conclude, the findings of this thesis contribute to advancing both pharmacological treatment and non-pharmacological treatment, as well as enhancing patient-centered care. The positive results of the PREDMETH trial offer patients an alternative first-line treatment option and highlight the need for shared-decision making in choosing the most appropriate treatment for each individual. The TIRED trial demonstrated the value of online mindfulness-based psychological support in reducing fatigue and improving QoL. Together these findings provide evidence for a more patient-centred and evidence-based approach to care. Future research should continue to build on these findings to address the remaining gaps in treatment and management for patients with sarcoidosis.

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The background is an abstract composition of layered, textured paper. A large, light beige piece of paper is at the top, with a smaller, darker beige piece layered underneath it on the left. A vibrant pinkish-red piece of paper is layered on the left side, and a darker red piece is at the bottom right. The entire composition is decorated with numerous watercolor splatters and dots in shades of pink, red, and beige, creating a soft, artistic feel.

Part V

Appendices

Summary

PART I: Introduction

Sarcoidosis is an inflammatory disease that affects multiple organs, with the lungs and lymphatic system being the most commonly involved, in up to 90% of patients. The cause of sarcoidosis is not fully understood, the current hypothesis suggest that both genetic predisposition and environmental factors contribute to its development. There is no single gold-standard diagnostic test for sarcoidosis. Diagnosis relies on a combination of compatible clinical and radiological findings, histological confirmation of granulomas, and the exclusion of alternative causes of granulomatous disease, such as infections, malignancies, or other immune-mediated conditions.

The clinical course and prognosis of sarcoidosis are highly variable. In pulmonary sarcoidosis, approximately half of patients achieve spontaneous remission and do not require treatment, particularly in the presence of mild symptoms and preserved lung function. Immunosuppressive treatment is indicated in cases with a high risk of mortality, permanent disability, or severe symptoms that negatively affect quality of life (QoL). Importantly, even in the absence of active inflammation, patients often experience general symptoms such as fatigue, psychological symptoms (including anxiety and depressive symptoms), and cognitive impairment. These manifestations highlight the need for a multidisciplinary approach to manage the diverse and variable manifestations of sarcoidosis.

Chapter 1 provides a general introduction to this thesis, outlining the clinical background of sarcoidosis, key challenges in patient care, and the rationale for the studies presented.

Chapter 2 provides an overview of a comprehensive care model and proposes the “ABCDE model” for patients with sarcoidosis, which includes (A) **A**ssessment, (B) **B**acking and support, (C) treatment of **C**omplaints and **C**omorbidities, (D) **D**isease-modifying therapies, and (E) collaboration with **E**xtrapulmonary specialists. This chapter emphasizes that regular reassessment and shared decision-making with patients are needed to optimize care delivery. Furthermore, it highlights the need for more research into both pharmacological and non-pharmacological interventions to improve patient outcomes and QoL.

Part II of this thesis focuses on improving pharmacological treatment strategies for patients with sarcoidosis. **Part III** focuses on improving quality of life for patients living with sarcoidosis. In **Part IV**, this thesis discusses the implications of the findings of this thesis and provides perspectives on future research.

PART II Improving pharmacological treatment for patients with sarcoidosis

Chapter 3 describes our perspective on the recently updated 2021 ERS clinical practice guidelines for the treatment of sarcoidosis, which represent an important shift towards a more patient-tailored approach in the management of sarcoidosis. Despite improvements in the understanding of disease pathogenesis, treatment options for sarcoidosis continue to rely on low-quality evidence. Even the strong recommendation for first-line treatment with corticosteroids is supported by low quality of evidence, underscoring the need for further research also into both first- and second-line options. In addition, chapter 3 addresses challenges in study design related to the heterogeneity of sarcoidosis, particularly with regard to patient selection and choice of endpoints. Overall, this correspondence aims to stimulate further high-quality research and promote patient-centred care in sarcoidosis management.

Chapter 4 reports the results of a retrospective cohort study that explored patient experiences with prednisone and methotrexate. Prednisone, the current first-line treatment, is often associated with significant side effects, whereas methotrexate, commonly used as second-line therapy, appears to have fewer side effects based on clinical observations, although no studies have directly compared the two medications. Patient-reported side effects were evaluated using a questionnaire. A significantly higher proportion of patients reported side effects with prednisone (78%) compared to methotrexate (49%). These findings suggest that methotrexate may have fewer side effects, although prospective confirmation is needed.

The research in this thesis was conducted during the coronavirus disease 2019 (COVID-19) pandemic. **Chapter 5** reviews the available evidence on sarcoidosis in relation to COVID-19. Most evidence consisted of case reports, case series, cohort studies, and registry data, from which no firm conclusions could be drawn. While it remained unclear whether sarcoidosis itself increases susceptibility to COVID-19, patients with moderate to severe pulmonary impairment appeared to be at higher risk of adverse outcomes and mortality. The impact of immunosuppressive

therapy on COVID-19 severity and vaccine response was also unclear. This chapter also discusses the role of telemedicine and home monitoring as promising strategies to ensure continuity of care during the pandemic.

Chapter 6 describes the design and rationale of the PREDMETH trial, a randomized controlled trial comparing prednisone and methotrexate as first-line treatment for pulmonary sarcoidosis. Current treatment guidelines recommend prednisone as the standard first-line therapy, however this is often associated with burdensome side effects that may impact quality of life. Methotrexate, currently used as second-line therapy, appears to be better tolerated, but has never been studied prospectively as first-line treatment. The design of the study was developed through a collaboration between clinicians, researchers, and patients and was conducted in 17 hospitals in the Netherlands. The primary outcome was the change in forced vital capacity (FVC), with secondary outcomes including home spirometry, patient-reported outcomes, side effects, and blood biomarkers. By combining clinical outcomes, home monitoring, and biomarker analyses, this study aimed to improve insights into treatment response, disease progression, and underlying disease mechanisms.

Chapter 7 reports the results of the PREDMETH trial, in which methotrexate proved to be noninferior to prednisone with respect to improvement in FVC% predicted over 24 weeks. The total number of adverse events was similar in both groups, however, after 24 weeks of treatment fewer side effects persisted in the methotrexate group. As expected, the side-effect profiles differed: prednisone was mainly associated with weight gain, insomnia, and increased appetite, whereas methotrexate was more often associated with nausea, fatigue, and abnormal liver function tests. Secondary endpoints, including lung function, symptoms, and quality of life were also noninferior for methotrexate compared to prednisone. These findings demonstrate that methotrexate is an effective and tolerable alternative to prednisone as first-line therapy in pulmonary sarcoidosis and underscore the importance of shared decision-making between physicians and patients when selecting the most appropriate initial treatment strategy.

PART III Improving quality of life for patients with sarcoidosis

In **Chapter 8**, the 'invisible' burden of sarcoidosis is addressed, including non-organ-specific manifestations such as fatigue, anxiety, depression, pain, cognitive dysfunction, and small-fiber neuropathy. These symptoms are highly prevalent, often persist even when there are no signs of organ-specific disease activity, and can have a major impact on the lives of patients and their families. The literature

is reviewed with regard to prevalence, impact, assessment, and treatment of non-organ manifestations. A discrepancy between patient- and physician-reported symptoms highlights the importance of routine assessment using patient-reported outcome measures (PROMs). Management should be multidisciplinary and primarily focus on non-pharmacological interventions, such as physical training, pulmonary rehabilitation, and psychological support, as disease-modifying therapy alone often does not adequately address these manifestations. Finally, the need for increased awareness, attention to socioeconomic factors, and further research into effective treatment strategies for non-organ-specific manifestations of sarcoidosis is underlined.

Chapter 9 focuses on fatigue as one of the most frequently reported and burdensome symptoms in patients with sarcoidosis and interstitial lung disease (ILD). The etiology of fatigue is complex and multifactorial, involving physical and mental components as well as predisposing, precipitating, and perpetuating factors. The assessment of fatigue using PROMs is discussed, emphasizing the importance of a structured and systematic evaluation. Given the limited evidence for both pharmacological and non-pharmacological treatment options, management of fatigue should be multidimensional and individually tailored. Key steps include optimization of treatment of the underlying disease, identification and treatment of reversible contributing factors, and the use of supportive interventions. A practical algorithm is proposed to guide clinicians in the assessment and management of fatigue.

Chapter 10 describes the results of the TIRED-trial, a randomized controlled trial that evaluated the effect of an online mindfulness-based cognitive therapy (eMBCT) program on fatigue in patients with sarcoidosis. In this trial, patients with stable sarcoidosis and fatigue were randomized to a supervised 12-week online eMBCT program or a control group receiving usual care. Patients in the eMBCT group experienced a clinically meaningful reduction in fatigue compared with the control group. In addition, improvements were observed in anxiety, depressive symptoms, mindfulness, and overall health status. Overall, eMBCT is an effective non-pharmacological treatment option for fatigue in patients with sarcoidosis and supports the role of psychological interventions within a multidisciplinary, patient-centered approach to care.

Following publication of the TIRED trial, subsequent correspondence raised questions regarding whether underlying causes, such as obstructive sleep apnea, had been excluded. The possibility that COVID-19 may have acted as a

confounding factor was also raised. **Chapter 11** addresses these questions. This chapter emphasizes the multifactorial nature of sarcoidosis-associated fatigue and clarifies that treatable causes had been carefully assessed and managed prior to study inclusion. Methodological considerations, including the potential impact of the COVID-19 pandemic and fatigue assessment are also discussed. Finally future directions for research are outlined.

Chapter 12 explores patient-driven perspectives on the care trajectory in sarcoidosis using a novel machine learning-driven approach. By analyzing a large collection of patient stories from a Dutch sarcoidosis online platform, topic modelling and sentiment analysis were applied to capture patients' experiences across the care pathway. This approach identified key themes, decision moments, and parallel care tracks inside and outside the hospital, as well as topics associated with positive and negative emotions. Most patient perspectives related to symptoms, disease-modifying treatment, and quality of life. A substantial part of living with sarcoidosis remains invisible in routine clinical care. Machine learning techniques can provide valuable insights into patient experiences, and integrating these insights into healthcare design may further improve patient-centered care in sarcoidosis.

PART IV DISCUSSION

In **chapter 13**, the general discussion places the findings in the context of existing literature and discusses their implications for future clinical care and research.

Samenvatting

Deel I: Introductie

Sarcoïdose is een inflammatoire aandoening, gekenmerkt door de vorming van granulomen, die in vrijwel alle organen kunnen voorkomen. De etiologie van sarcoïdose is complex en nog niet volledig opgehelderd. De huidige inzichten gaan ervan uit dat een onbekend antigeen leidt tot een overmatige immuunrespons bij personen met een bepaalde genetische vatbaarheid.

Aangezien de longen bij circa 90% van de patiënten zijn aangedaan, is de longarts vaak de centrale coördinator van de zorg voor patiënten met sarcoïdose. Patiënten kunnen zich presenteren met uiteenlopende klachten. Bij pulmonale sarcoïdose zijn dit vaak specifieke klachten zoals dyspnoe, hoesten en malaise. Dit maakt het stellen van de diagnose uitdagend. Er bestaat geen gouden standaardtest waarmee sarcoïdose kan worden vastgesteld. Voor het stellen van de diagnose moet aan drie belangrijke criteria worden voldaan: **(I)** een passende kliniek en radiologie, **(II)** het aantonen van granulomen in een biopsie en **(III)** het uitsluiten van andere aandoeningen die een granulomateuze ontsteking kunnen veroorzaken, zoals infecties, maligniteiten of andere immuun gemedieerde aandoeningen.

Patiënten met pulmonale sarcoïdose hoeven niet altijd behandeld te worden. Dit is afhankelijk van de uitgebreidheid van de pulmonale afwijkingen, de achteruitgang van de longfunctie en de ernst van de symptomen. Bij ongeveer de helft van de patiënten zal de inflammatie in de loop van de tijd spontaan afnemen, zonder behandeling met immunosuppressiva. Behandeling is geïndiceerd wanneer er sprake is van orgaandysfunctie met een verhoogd risico op mortaliteit of permanente morbiditeit, of bij ernstige symptomen die de kwaliteit van leven negatief beïnvloeden.

Naast orgaan specifieke klachten hebben patiënten ook vaak last van algemene symptomen, zoals vermoeidheid, angst-depressieve klachten en geheugenverlies. Deze klachten reageren doorgaans onvoldoende op immunosuppressieve behandeling en blijven vaak bestaan, zelfs wanneer er geen tekenen van actieve inflammatie meer zijn. Daarom is een multidisciplinaire benadering, waarin niet alleen wordt gekeken naar farmacologische behandeling maar ook naar ondersteunende interventies, van groot belang om symptomen en kwaliteit van leven te verbeteren.

Hoofdstuk 1 vormt een algemene inleiding waarin de achtergrond en context van dit proefschrift worden geschetst en dient als basis voor de daaropvolgende delen.

In **hoofdstuk 2** wordt de huidige kennis rondom verschillende aspecten van zorg samengevat en wordt het 'ABCDE'-model voorgesteld voor integrale en multidisciplinaire zorg, bestaande uit **(A) Assessment**, **(B) Backing and support** (begeleiding en ondersteuning), **(C) treatment of Complaints and Comorbidities** (behandeling van klachten en comorbiditeit), **(D) Disease-modifying therapies** (immunosuppressieve behandeling) en **(E) collaboration with Extrapulmonary specialists** (samenwerking met extrapulmonale specialisten). Daarbij wordt benadrukt dat regelmatige beoordeling van klachten en shared-decision making belangrijk zijn om de zorg te optimaliseren.

In **deel II** van dit proefschrift staat het optimaliseren van farmacologische behandeling voor patiënten met sarcoïdose centraal. In **deel III** ligt de focus op het verbeteren van kwaliteit van leven. Tot slot worden in **deel IV** de bevindingen van dit proefschrift besproken in de context van de bestaande literatuur en worden suggesties gedaan voor toekomstig onderzoek.

Deel II Het optimaliseren van farmacologische behandeling voor patiënten met sarcoïdosis

Hoofdstuk 3 beschrijft onze visie op de in 2021 gepubliceerde European Respiratory Society (ERS)-richtlijn voor de behandeling van sarcoïdose. Deze richtlijn laat een belangrijke verschuiving zien naar een meer patiëntgerichte benadering van zorg. Ondanks toegenomen inzicht in de pathogenese zijn de richtlijnaanbevelingen voor de behandeling van sarcoïdose nog grotendeels gebaseerd op wetenschappelijk onderzoek van lage kwaliteit. Zelfs de sterke aanbeveling voor eerstelijnsbehandeling met corticosteroiden is gebaseerd op lage kwaliteit. Onderzoek bij patiënten met sarcoïdose is vaak uitdagend vanwege de heterogeniteit van de ziekte en het variabele ziekte beloop. Dit leidt tot uitdagingen bij patiëntselectie en de keuze van geschikte eindpunten. In de afgelopen jaren is veel onderzoek verricht naar nieuwe derdelijnsbehandelingen voor patiënten met refractaire sarcoïdose. Deze patiënten hebben echter vaak een ander immunologisch profiel dan behandelnaïeve patiënten, waardoor idealiter meer onderzoek zou moeten worden verricht naar eerste- en tweedelijnsbehandelopties bij behandelnaïeve patiënten.

De huidige eerstelijnsbehandeling met prednison gaat vaak gepaard met vervelende bijwerkingen, die de kwaliteit van leven negatief kunnen beïnvloeden. Methotrexaat, dat op dit moment in de richtlijn wordt aanbevolen als tweedelijnsbehandeling, lijkt mogelijk beter verdragen te worden dan prednison. Deze behandelingen zijn echter nog niet direct met elkaar vergeleken. In **hoofdstuk 4** worden de resultaten gepresenteerd van een retrospectieve studie naar patiëntervaringen met prednison en methotrexaat. Tijdens een jaarlijkse patiëntenvoorlichtingsbijeenkomst over sarcoïdose in het Erasmus Universitair Medisch Centrum in 2019 zijn patiënten gevraagd een vragenlijst in te vullen over medicatiegebruik en hun ervaringen met prednison en methotrexaat. Hieruit blijkt dat significant meer patiënten bijwerkingen hebben ervaren bij het gebruik van prednison (78%) dan bij methotrexaat (49%). Deze bevinding onderstreept de noodzaak voor verder onderzoek naar alternatieve behandelingen voor prednison.

Tijdens het onderzoek in dit proefschrift vond de COVID-19-pandemie plaats. **Hoofdstuk 5** geeft een overzicht van de beschikbare literatuur over het risico op COVID-19-infecties bij patiënten met sarcoïdose. De literatuur was beperkt tot casusbeschrijvingen, casusseries, cohortstudies en registerdata, waardoor geen specifieke aanbevelingen kunnen worden gedaan. Hoewel onduidelijk blijft of sarcoïdose zelf de vatbaarheid voor COVID-19 verhoogt, lijken patiënten met matige tot ernstige pulmonale functiestoornissen een verhoogd risico te hebben op ongunstige uitkomsten en mortaliteit. De invloed van immunosuppressieve therapie op de ernst van COVID-19 en de vaccinrespons is nog onvoldoende duidelijk. Daarnaast zijn de meeste gegevens afkomstig uit onderzoek bij andere inflammatoire aandoeningen. In dit hoofdstuk worden ook de mogelijkheden van thuismonitoring besproken om de continuïteit van zorg tijdens de pandemie te waarborgen.

Hoofdstuk 6 beschrijft het studieontwerp en de doelstellingen van de PREDMETH-studie, een Nederlandse multicenterstudie waarin de effectiviteit van methotrexaat en prednison met elkaar is vergeleken. De studie is opgezet als een gerandomiseerde non-inferioriteitstudie, met als doel aan te tonen dat methotrexaat net zo effectief is als prednison, maar gepaard gaat met minder bijwerkingen. Bij de studieopzet zijn klinici, onderzoekers en patiënten betrokken geweest. Het primaire eindpunt van de studie is het verschil in geforceerde vitale capaciteit (FVC) na 24 weken, waarbij een non-inferioriteitsmarge van 5% is gehanteerd. Secundaire eindpunten zijn patiëntgerapporteerde uitkomsten, bijwerkingen en biomarkers in het bloed. Als onderdeel van deze studie is

patiënten daarnaast gevraagd wekelijks thuispirometrie te verrichten en vragenlijsten in te vullen met betrekking tot symptomen en bijwerkingen, om zo meer gedetailleerd inzicht te verkrijgen in het effect van de behandeling op ziektebeloop en bijwerkingen.

In **hoofdstuk 7** worden de resultaten van de PREDMETH-studie beschreven. In deze studie is aangetoond dat methotrexaat non-inferieur is ten opzichte van prednison voor de behandeling van pulmonale sarcoïdose. De snelheid van effect verschilt tussen beide behandelingen: prednison heeft een snel effect na vier weken, dat daarna nagenoeg stabiel blijft, terwijl in de methotrexaatgroep een meer geleidelijke verbetering wordt gezien. Na 24 weken werd geen verschil in geforceerde vitale capaciteit (FVC) tussen beide groepen gevonden. Het totale aantal bijwerkingen is in beide groepen vergelijkbaar; na 24 weken behandeling komen echter minder aanhoudende bijwerkingen voor in de methotrexaatgroep. Zoals verwacht verschilt de aard van de bijwerkingen tussen beide medicamenten. Bij prednison worden met name gewichtstoename, slapeloosheid en toegenomen eetlust gerapporteerd, terwijl methotrexaat vaker gepaard gaat met misselijkheid, vermoeidheid en afwijkingen in levertesten. Ook alle secundaire eindpunten, waaronder diffusiecapaciteit, symptomen en kwaliteit van leven, zijn non-inferieur voor methotrexaat ten opzichte van prednison. Deze studie laat zien dat methotrexaat een goed alternatief is voor prednison bij de behandeling van pulmonale sarcoïdose. In de toekomst zal shared decision-making tussen arts en patiënt steeds belangrijker worden om de optimale behandeling op individueel niveau te kiezen.

Deel III: Verbetering van kwaliteit van leven bij sarcoïdose

Sarcoïdose gaat frequent gepaard met algemene, niet-orgaanspecifieke symptomen, waaronder vermoeidheid, angst- en depressieve klachten, pijn en geheugenverlies. Deze symptomen zijn veelal onzichtbaar voor de omgeving, wat kan bijdragen aan een gevoel van onbegrip bij patiënten. **Hoofdstuk 8** beschrijft deze symptomen, de wijze waarop zij kunnen worden herkend en de beschikbare behandelmogelijkheden. In de literatuur wordt vaak een discrepantie beschreven tussen arts- en patiëntgerapporteerde prevalentie van deze symptomen, waarbij artsen doorgaans lagere prevalenties rapporteren. Dit benadrukt het belang van patiëntgerapporteerde uitkomsten in de evaluatie en follow-up van sarcoïdose. Aangezien deze symptomen vaak onvoldoende reageren op immunosuppressieve behandeling en kunnen persisteren ondanks het ontbreken van actieve ziekteactiviteit, is een multidisciplinaire

benadering aangewezen. Hierbij dient in eerste instantie aandacht te zijn voor ondersteunende, niet-farmacologische interventies, zoals fysieke training, revalidatie en psychologische ondersteuning.

Een van de meest invaliderende en frequent voorkomende symptomen bij sarcoïdose is vermoeidheid, met een grote negatieve impact op het dagelijks leven. **Hoofdstuk 9** beschrijft de etiologie, beïnvloedende factoren en behandelopties van vermoeidheid bij patiënten met sarcoïdose en andere interstitiële longaan- doeningen. Er bestaat geen uniforme definitie van vermoeidheid; vaak wordt onderscheid gemaakt tussen mentale en fysieke componenten. De etiologie van vermoeidheid is complex en multifactorieel, waarbij fysiologische, psychologische en gedragsmatige factoren een rol spelen. Gezien deze multifactoriële aard wordt in dit hoofdstuk een behandelalgoritme voorgesteld, waarbij de eerste stap bestaat uit het optimaliseren van de behandeling van de onderliggende ziekte en het uitsluiten van medicatiegerelateerde bijwerkingen. Daarnaast dienen onderliggende aandoeningen, zoals slaapapneu, en relevante comorbiditeiten systematisch te worden uitgesloten en behandeld. Afhankelijk van de dominante klachten kan verwijzing naar psychologische ondersteuning, fysiotherapie of revalidatie en sociale begeleiding worden overwogen. Wanneer niet-farmacologische interventies onvoldoende effect hebben, kan farmacologische behandeling worden overwogen; kleine studies suggereren een mogelijk effect van neurostimulantia, zoals methylfenidaat, hoewel deze middelen off-label worden toegepast. Samenvattend is een integrale, multidisciplinaire en persoonsgerichte aanpak noodzakelijk voor de behandeling van vermoeidheid bij sarcoïdose. Toekomstig onderzoek is nodig om deze aanpak verder te onderbouwen en te optimaliseren.

Ook vanuit de Nederlandse patiëntenvereniging (sarcoidose.nl) wordt vermoeidheid consequent benoemd als een van de meest belastende symptomen bij sarcoïdose. Mede op basis van deze duidelijke patiëntbehoefte is een subsidie verkregen om gericht onderzoek te doen naar het effect van een twaalf weken durende online mindfulness-based cognitieve therapie (eMBCT) op vermoeidheid bij patiënten met sarcoïdose, de TIRED-studie.

Hoofdstuk 10 bespreekt de resultaten van deze gerandomiseerde multicenter- studie. Aan deze studie hebben patiënten met significante vermoeidheid deelgenomen, waarbij de sarcoïdosebehandeling gedurende de voorafgaande drie maanden stabiel is gebleven. Deelnemers zijn gerandomiseerd naar deelname aan het eMBCT-programma of gebruikelijke zorg. In de eMBCT-groep is een klinisch relevante afname van vermoeidheid gezien ten opzichte van de controlegroep.

Daarnaast zijn verbeteringen waargenomen in andere relevante patiëntuitkomsten, waaronder angst- en depressieve symptomen, toegenomen mindfulness en een verbeterde kwaliteit van leven. Deze resultaten laten zien dat eMBCT een effectieve behandeloptie is voor vermoeidheid bij patiënten met sarcoïdose.

Na de publicatie van de TIRED-studie is een commentaar ingezonden waarin vragen zijn gesteld over het al dan niet systematisch uitsluiten van onderliggende oorzaken van vermoeidheid, waaronder obstructieve slaapapneu. **Hoofdstuk 11** reageert op deze vragen. Voorafgaand aan deelname aan de TIRED-studie zijn behandelbare oorzaken uitgesloten dan wel eerst behandeld. In dit hoofdstuk wordt een gestructureerd algoritme gepresenteerd voor de beoordeling en behandeling van vermoeidheid bij patiënten met sarcoïdose.

Een groot deel van het leven met sarcoïdose speelt zich af buiten het zicht van het ziekenhuis en blijft in de klinische praktijk vaak onzichtbaar. **Hoofdstuk 12** beschrijft een studie naar de ervaringen van patiënten met sarcoïdose gedurende hun zorgtraject, uitgevoerd met behulp van een innovatieve, op machine learning gebaseerde benadering. Hiervoor is gebruikgemaakt van berichten afkomstig van een Nederlands online sarcoïdoseplatform. Met behulp van topic modelling zijn de berichten geclusterd in onderwerpen, waarna een sentimentanalyse is uitgevoerd om het overwegend positieve, negatieve of neutrale sentiment per topic te bepalen. Deze bevindingen zijn vervolgens geverifieerd, doordat onafhankelijke onderzoekers de sleutelwoorden en de meest relevante berichten hebben beoordeeld. Deze bevindingen zijn daarna gelabeld en gevisualiseerd in een overzicht van het patiëntentraject (patient journey map). De meeste patiëntperspectieven hebben betrekking op symptomen (voornamelijk negatief sentiment), immunosuppressieve medicatie (overwegend neutraal sentiment) en kwaliteit van leven (gemengd sentiment). Deze studie laat zien dat een innovatief, op machine learning gebaseerd algoritme een waardevolle methode is om grootschalige patiëntverhalen te analyseren en inzicht te verkrijgen in het patiëntperspectief op gezondheid en zorg.

Deel IV: Discussie

In **hoofdstuk 13**, de algemene discussie, worden de belangrijkste bevindingen geplaatst in de context van de bestaande literatuur en worden de implicaties voor toekomstige klinische zorg en onderzoek besproken.

PhD portfolio

Summary of PhD training and teaching

Name PhD student: V (Vivienne) Kahlmann

Erasmus MC department: Pulmonary Medicine

Research school: Molecular Medicine

PhD period: 2020 - 2025

Promotor: Prof. Dr. Marlies Wijsenbeek

Co-promotor: Dr. Catharina Moor

ECTS: 51.0

1.PhD training	Year	Workload ECTS
General courses, seminars and workshops		
Systematic literature retrieval in Pubmed	2019	0.3
Good clinical practice (GCP)	2019	0.3
EndNote workshop	2020	0.2
Research integrity	2020	0.3
Biostatistical Methods I: Basic Principles Part A (NIHES)	2020	1.0
Basic Introduction SPSS	2020	1.0
ERS Interstitial Lung disease course	2020	0.5
Biomedical English writing course	2021	1.5
Basic course Rules and Organization for Clinical researcher	2021	1.5
Interstitial lung disease (ILD) winter course, Davos	2021	1.0
Advanced Immunology Course	2021	0.9
NRS National Lung Course and Young Investigator Symposia	2021	5.0
Advanced Clinical Trials	2022	1.9
Immunology course, University Medical Center Groningen, The Netherlands	2025	1.0
(Inter)national scientific presentations and conferences		
Networked Science Symposium, Rotterdam	2019	0.2
Dutch Lung Foundation – Amersfoort (<i>oral presentation</i>)	2020	0.3
National Sarcoidosis Patient Association Day – Virtual (<i>oral presentation</i>)	2020	0.3

	Year	Workload ECTS
European Respiratory Society (ERS) Conference – Virtual	2020	1.0
National Sarcoidosis Patient Association Day – Putten, The Netherlands (<i>oral presentation</i>)	2021	0.3
Dutch Lung Conference – virtual (<i>1 oral presentation, 1 poster presentation</i>)	2021	1.3
ERS Conference – virtual (<i>oral presentation</i>)	2021	1.5
Breath symposium 'ERS highlights' – Ermelo, the Netherlands (<i>poster presentation</i>)	2021	0.3
Science Day Pulmonary Department Erasmus MC, Rotterdam, The Netherlands	2022	0.2
Dutch Lung Conference – Utrecht, The Netherlands	2022	0.5
American Thoracic Society (ATS) conference – San Francisco, U.S.A. (<i>2 oral presentations, 1 poster presentation</i>)	2022	2.0
Dutch Lung Conference – Utrecht, the Netherlands	2022	0.5
ERS conference – Barcelona, Spain (<i>2 oral presentations</i>)	2022	1.5
Turkish Pulmonology Conference – Antalya, Turkey/online (<i>oral presentation</i>)	2023	0.5
ATS conference – Washington, U.S.A. (<i>1 oral presentation</i>)	2023	1.5
World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG) conference – Stockholm, Sweden (<i>2 oral presentations</i>)	2023	2.0
ERS conference, Vienna, Austria (<i>2 oral presentations</i>)	2024	1.5
WASOG conference – Agra, India (<i>oral presentation</i>)	2024	1.5
WASOG Task Force Meeting (<i>oral presentation</i>)	2025	0.5
Turkish Pulmonology Conference – Antalya, Turkey/online (<i>oral presentation</i>)	2025	0.5
Dutch pulmonologist conference (NVALT), Papendal, The Netherlands (<i>oral presentation</i>)	2025	0.5
ATS conference – San Francisco, U.S.A. (<i>1 oral presentation, 1 poster presentation</i>)	2025	1.5
Foundation of Sarcoidosis Research (FRS) - online patient summit (<i>oral presentation</i>)	2025	0.5

	Year	Workload ECTS
WASOG conference – Ottawa, Canada (3 oral presentations)	2025	1.5
ERS conference – Amsterdam, the Netherlands (<i>1 oral presentation, 1 poster presentation</i>)	2025	1.5
2. Teaching		
Lecturing		
Tutor, Medicine Bachelor Year 1 (10 interactive lessons)	2020	1.5
Workshop blood gas analysis (1 st year medicine students)	2020-2025	1.0
Interactive lecture: the Dyspnoeic patient (4 th year medicine students)	2021-2024	1.0
Coaching		
Coach Medicine Students	2020-2024	1.0
Supervising		
Co-Supervising PhD student	2024-Present	1.5
3. Other research related activities		
Movies, Podcasts and interviews		
Movie Sterk Patient Participation award	2021	0.2
Movie update ERS conference	2022	0.1
Podcast Lancet Respiratory Medicine	2022	0.1
Movie update ERS conference	2024	0.1
Interviews for Dutch Medical Journals	2022-2025	0.2
Reviewing		
Peer reviewer for international journals	2020-2025	2.0
Scientific Committees		
Co-chair, Dutch Sarcoidosis Guideline – NVALT	2024	1.0
Workgroup Member, Guideline for Toxicity Monitoring of Glucocorticosteroids and DMARDs – Federation of Medical Societies (FMS)	2024	1.0
Workgroup member of the ATS Scientific programming committee Assembly on Behavioural Science and Health Services Research	2025	0.5

	Year	Workload ECTS
4. Awards & Grants		
Sarcoidose.nl PhD award (Bouwhuisprijs)	2020	
Nomination Sterk Patient Participation Award – Dutch Lung foundation	2021	
International Trainee Scholarship Award, ATS conference, San Francisco, U.S.A.	2022	
Abstract Scholarship Award, ATS, San Francisco (sponsored by Foundation of Sarcoidosis Research (FSR))	2022	
Best Abstract award in Assembly 12 (ILD), ERS conference, Vienna, Austria	2024	
Abstract Scholarship Award, WASOG conference, Agra, India	2024	
NRS Young Investigator Travel Grant	2024	
International Trainee Scholarship Award, ATS conference, San Francisco, U.S.A.	2025	
NRS Young Investigator Travel Grant	2025	
Abstract Scholarship Award/best clinical presentation award WASOG conference, Ottawa, Canda	2025	
Pilot Grant – Foundation for Sarcoidosis	2025	
Harry Groen prijs	2025	
Total ECTS		51.0

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About the Author

Vivienne Kahlmann was born on June 27, 1988, in Rotterdam, the Netherlands. From an early age, she expressed the ambition to become a doctor, inspired in part by her parents, both of whom worked as nurses. After graduating from secondary school at Sint Laurens College in Rotterdam in 2006, she initially studied Health Sciences before being admitted to medical school at Erasmus University in Rotterdam.

As a medical student, she was involved in committees of the medical student association, the student council, and teaching activities. She remained active in sports including softball and lacrosse, and worked part-time in healthcare. During her internships, including a three-month elective in Ecuador, she developed a broad interest in medical specialties. She completed her master's thesis on Guillain-Barré syndrome, resulting in her first scientific publications and initiating her interest in clinical research.

After graduating from medical school in 2014, she worked as a physician in the department of internal medicine at Sint Franciscus Hospital in Rotterdam and Amphia Hospital in Breda, where she developed a growing interest in pulmonary medicine. In 2016, she started her residency training in respiratory medicine at Erasmus Medical Center. Throughout her training, her interest in clinical research remained strong. In 2021, she began a PhD project supervised by Prof. dr. M.S. Wijsenbeek (promotor) and Dr. C.C. Moor (co-promotor), focusing on optimizing treatment and outcomes for patients with sarcoidosis and reflecting her interest in multidisciplinary care and collaboration. The research conducted for this thesis was presented at international conferences, including the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG). She received several awards and scholarships, including the ATS International Trainee Scholarship (2022, 2025), the best ERS abstract award in interstitial lung disease (2024), and the Harry Groen prijs (2025). In 2025, she received a grant from the Foundation for Sarcoidosis Research to continue research on optimizing treatment for patients with sarcoidosis.

In November 2025, she completed her training in pulmonary medicine and started working at Leiden University Medical Center as a pulmonologist focusing on interstitial lung diseases, combining clinical care with research. She also continues to work one day per week at Erasmus Medical Center, remaining active in clinical research in sarcoidosis.

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Dit proefschrift is het resultaat van een mooi en leerzaam traject, waarin samenwerking centraal stond. Met veel enthousiasme heb ik gewerkt aan uiteenlopende projecten. Ik heb vele mensen ontmoet die mij kansen gaven, in mij geloofden en met wie ik intensief heb samengewerkt. In dit laatste deel van mijn proefschrift wil ik graag mijn dank uitspreken aan allen die aan dit traject hebben bijgedragen.

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Afdeling longziekten Erasmus MC

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PREDMETH-studie groep

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