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Early View

Task force report

ERS clinical practice guidelines on treatment of sarcoidosis

Robert P. Baughman, Dominique Valeyre, Peter Korsten, Alexander G. Mathioudakis, Wim A. Wuyts, Athol Wells, Paola Rottoli, Hiliaro Nunes, Elyse E. Lower, Marc A. Judson, Dominique Israel-Biet, Jan C. Grutters, Marjolein Drent, Daniel A. Culver, Francesco Bonella, Katerina Antoniou, Filippo Martone, Bernd Quadder, Ginger Spitzer, Blin Nagavci, Thomy Tonia, David Rigau, Daniel R. Ouellette

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ERS clinical practice guidelines on treatment of sarcoidosis

Robert P. Baughman MD (1, 25)

Dominique Valeyre MD (2)

Peter Korsten MD (3)

Alexander G. Mathioudakis MD (4)

Wim A. Wuyts MD (5)

Athol Wells MD (6)

Paola Rottoli MD (7)

Hiliaro Nunes MD (8)

Elyse E. LowerMD (1)

Marc A. Judson MD (9)

Dominique Israel-Biet MD (10)

Jan C. Grutters MD (11, 12)

Marjolein Drent MD PhD (11,13, 14)

Daniel A. Culver DO (15)

Francesco Bonella MD (16)

Katerina Antoniou MD (17)

Filippo Martone (18)

Bernd Quadder (19)

Ginger Spitzer (20)

Blin Nagavci MD, MSc. (21)

Thomy Tonia (22)

David Rigau (23)

Daniel R. Ouellette MD (24)

1. Department of Medicine, University of Cincinnati Medical Center, Cincinnati, OH, USA
2. INSERM UMR 1272, Université Sorbonne Paris Nord; APHP, Hôpital Avicenne, Bobigny; Groupe Hospitalier Paris-Saint Joseph, Paris, France

3. Department of Nephrology and Rheumatology, University Medical Center Göttingen, Göttingen, Germany
North West Lung Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, and Division of Infection, Immunity and Respiratory Medicine, The University of Manchester, UK and supported by an ERS Fellowship in Guidelines Methodology (MTF 2015-1) and by the National Institute of Health Research Manchester Biomedical Research Center (NIHR Manchester BRC.
5. Unit for interstitial lung diseases, Dept respiratory medicine, University hospitals Leuven, Belgium
6. Royal Hospital Brompton, London, UK
7. Specialization School of Respiratory Diseases, Dept of Medical, Surgical and Neurological Sciences, Siena University, Siena, Italy
8. INSERM UMR 1272, Université Sorbonne Paris Nord; Service de Pneumologie, Centre de Référence des Maladies Pulmonaires Rares, APHP, Hôpital Avicenne, Bobigny, France
9. Department of Medicine, Albany Medical College, Albany NY, USA
10. Université de Paris, Centre de compétences Maladies rares pulmonaires, AP-HP, Hôpital Européen Georges Pompidou, Paris, France.
11. ILD Center of Excellence, Department of Pulmonology, St. Antonius Hospital, Nieuwegein, The Netherlands.
12. Division of Heart & Lungs, University Medical Center Utrecht, Utrecht The Netherlands
13. Department of Pharmacology and Toxicology, Faculty of Health and Life Sciences, Maastricht University, Maastricht, the Netherlands
14. ild care foundation research team, Ede, the Netherland
15. Cleveland Clinic, Cleveland, OH, USA
16. Center for Interstitial and Rare Lung Diseases, Pneumology Department, Ruhrlandklinik, University Hospital, University of Essen, Essen, Germany.
17. Department of Respiratory Medicine, Laboratory of Molecular and Cellular Pneumonology, Medical School, University of Crete, Heraklion, Greece
18. Amici Contro la Sarcoidosi Italia ONLUS, Italy
19. Deutsche Sarkoidose-Vereinigung e.V. (DSV) Germany
20. Foundation for Sarcoidosis Research, Chicago, IL, USA
21. Institute for Evidence in Medicine, Medical Center and Faculty of Medicine, University of Freiburg, Freiburg, Germany
22. Institute of Social and Preventive Medicine, University of Bern, Switzerland
23. Cochrane Iberoamerica. Barcelona, Spain.
24. Henry Ford Hospital, Detroit, MI, USA
25. Corresponding author Robert P. Baughman MD, 200 Albert Sabin Way, Room 1001, University of Cincinnati Medical Center, Cincinnati, OH, USA 42567. Email bob.baughman@uc.edu

Abstract

Background: The major reasons to treat sarcoidosis are to lower the morbidity and mortality risk or to improve quality of life (QoL). The indication for treatment varies depending on which manifestation is the cause of symptoms: lungs, heart, brain, skin, or other manifestations. While glucocorticoids (GC) remain the first choice for initial treatment of symptomatic disease, prolonged use is associated with significant toxicity. GC-sparing alternatives are available. The presented treatment guideline aims to provide guidance to physicians treating the very heterogenous sarcoidosis manifestations.

Materials and methods A European Respiratory Society Task Force (TF) committee composed of clinicians, methodologists, and patients with experience in sarcoidosis developed recommendations based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology. The committee developed eight PICO (Patients, Intervention, Comparison, Outcomes) questions and these were used to make specific evidence-based recommendations.

Results The TF committee delivered twelve recommendations for seven PICOs. These included treatment of pulmonary, cutaneous, cardiac, and neurologic disease as well as fatigue. One PICO question regarding small fiber neuropathy had insufficient evidence to support a recommendation. In addition to the recommendations, the committee provided information on how they use alternative treatments, when there was insufficient evidence to support a recommendation.

Conclusions There are many treatments available to treat sarcoidosis. Given the diverse nature of the disease, treatment decisions require an assessment of organ involvement, risk for significant morbidity, and impact on QoL of the disease and treatment.

Message: An evidence based guideline for treatment of sarcoidosis is presented. The panel used the GRADE approach and specific recommendations are made. A major factor in treating patients is the risk of loss of organ function or impairment of quality of life.

A. Introduction

The previous international statement for diagnosis and management of sarcoidosis was developed in 1999 by the European Respiratory Society (ERS), American Thoracic Society (ATS), and the World Association of Sarcoidosis and Other Granulomatous disease (WASOG)[1;2]. The diagnostic approach has recently been updated [3]. Over time, there has been a shift on emphasis on who, when, and with what to treat sarcoidosis patients [4;5] The decision of who and when to treat an individual sarcoidosis patient depends on two major factors: risk for death or organ failure and impairment of quality of life (QoL). About five percent of patients with sarcoidosis die from the disease [4;6-8]. Pulmonary and cardiac disease are the most common reasons for death from sarcoidosis [9]. Irreversible organ damage to brain, eyes, or kidneys can also cause significant morbidity [10]. Recent studies have identified features associated with increased risk for death from pulmonary disease, including pulmonary hypertension, reduced lung function, and pulmonary fibrosis [6;11-13]. Anti-inflammatory therapy for less severe but impaired patients may prevent progression to irreversible disease [10]. Both sarcoidosis associated fatigue (SAF), a symptom not associated with a specific organ manifestation, and small-fiber neuropathy (SFN) associated symptoms, are encountered in a significant number of sarcoidosis patients [14-17], and treatment is a high priority for these patients [18].. While fatigue is common, we looked specifically at fatigue severe enough to consider treatment (troublesome fatigue).

A committee was developed by the ERS to develop new guidelines for treating sarcoidosis using a standardized methodology [19]. The committee systematically reviewed treatment for pulmonary, cutaneous, cardiac, and neurologic manifestations as well as sarcoidosis-associated fatigue and SFN. There have been several proposed terms to describe the clinical phenotype of sarcoidosis patients

including stage (which refers to chest x-ray pattern as described by Scadding [20]), activity (ongoing inflammation), and acute versus chronic [21]. Most of the papers reviewed did not offer specific criteria of the patients treated. We chose to make our recommendations based on presence of symptomatic disease unless otherwise noted. Specific recommendations for each PICO using GRADE criteria are shown in **Table 1**. The committee found insufficient information to make recommendations for other organ involvement. While eye involvement occurs in a significant number of cases, there are few studies specifically regarding treatment of ocular sarcoidosis [22-25] and the committee did not feel this could be studied at this time. There have been some studies reporting on the use of adalimumab for non-infectious uveitis including sarcoidosis [26;27]. However, these studies did not specifically analyze ocular sarcoidosis. To date, few studies have reported specifically on the effectiveness of adalimumab for ocular sarcoidosis [22;24;28].

Table 2 summarizes the anti-inflammatory drugs used in treatment of sarcoidosis. More details regarding dosage, major toxicity, and monitoring are made in Supplement 1. General comments regarding individual therapies for sarcoidosis are reviewed in supplement S-1. We did not search studies that specifically evaluated dosing, monitoring, or compared one versus another treatment duration for any form of sarcoidosis. Several studies have noted that relapse of symptomatic disease occurs in a significant number of patients upon withdrawal of therapy after one to two years. The reported rate of relapse of disease upon GC withdrawal after two years of initial therapy ranges from 20 to 80% [29-32]. Withdrawal of methotrexate therapy after two additional years for chronic sarcoidosis was associated with an eighty percent reinstitution of systemic therapy [33]. For patients treated with infliximab for advanced sarcoidosis, discontinuation of treatment after six to twelve months was associated with relapse of disease more than half the time [34-36]. These observations have led to the comment that

patients may have modifications of treatment to avoid toxicity and the need for continued successful treatment should be reevaluated every one to two years [4].

For the most part, the analysis was restricted to anti-inflammatory treatments. Use of agents to treat complications of sarcoidosis such as pulmonary hypertension and hydrocephalus were not evaluated. Nor did we analyze the results of transplantation, especially lung or heart transplantation, which can be an important part of management of advanced disease [37-39].

Table 1

Task Force Recommendations

PICO number		Recommendation
1	***In patients with pulmonary sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?***	For untreated patients with major involvement from pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis, we recommend the introduction of glucocorticoid treatment, to improve and/or preserve FVC and QoL. (Strong recommendation, low quality of evidence).
2	***In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?***	For patients with 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, we suggest the addition of methotrexate to improve and/or preserve FVC and QoL. (Conditional recommendation, very low quality of evidence).
		For patients with 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, we suggest the addition of infliximab to improve and/or preserve FVC and QoL. (Conditional recommendation, low quality of evidence).
3	***In patients with cutaneous sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?***	For patients with cutaneous sarcoidosis and cosmetically important active skin lesions which cannot be controlled by local treatment, we suggest oral glucocorticoids be considered to reduce skin lesions. (Conditional recommendation, very low quality of evidence).

4	***In patients with cutaneous sarcoidosis, should one add other immunosuppressive treatment when treatment with glucocorticoids has not been effective?***	For patients with cutaneous sarcoidosis who have been treated with glucocorticoids and/or other immunosuppressive agents and have continued cosmetically important active skin disease, we suggest the addition of infliximab compared to no additional treatment to reduce skin lesions (conditional recommendation, low quality of evidence).
5	***In patients with clinically relevant cardiac sarcoidosis, should glucocorticoids with or without other immunosuppressives versus no immunosuppression be used?***	For patients with evidence of functional cardiac abnormalities, including heart block, dysrhythmias, or cardiomyopathy, we recommend the use of glucocorticoids (with or without other immunosuppressives) (strong recommendation, very low quality of evidence).
6	***In patients with neurosarcoidosis, should immunosuppressive treatment be used versus no immunosuppressive treatment?***	For patients with clinically significant neurosarcoidosis, we recommend treatment with glucocorticoids (Strong recommendation, very low quality of evidence).
		For patients with neurosarcoidosis that have been treated with glucocorticoids and have continued disease, we suggest the addition of methotrexate (conditional recommendation, very low quality of evidence).
		For patients with neurosarcoidosis that have been treated with glucocorticoids and a second-line agent (methotrexate, azathioprine, mycophenolate mofetil) and have continued disease, we suggest the addition of infliximab (conditional recommendation, very low quality of evidence).

7	***In patients with sarcoidosis associated fatigue, should immunosuppressants, neurostimulants, exercise, or other treatments be used versus no treatment for fatigue?***	In patients with sarcoidosis who have troublesome fatigue, we suggest a pulmonary rehabilitation program and/or inspiratory muscle strength training for 6-12 weeks to improve fatigue. (Conditional recommendation, low quality of evidence).
		In patients with sarcoidosis who have troublesome fatigue that is not related to disease activity, and after consideration of a pulmonary exercise or rehabilitation program, we suggest the use of d-methylphenidate or armodafinil for 8 weeks to tests its effect on fatigue and tolerability (Conditional recommendation, low quality of evidence).
8	***In sarcoidosis patients with small fiber neuropathy, should immunosuppressants or intravenous immunoglobulin be prescribed versus no treatment?***	**No recommendations were made for this PICO question due to a lack of sufficient evidence.**

Table 2

Immunosuppressive therapies for sarcoidosis

Drug	Usual Dosage	Major Toxicity	Recommended monitoring	Comments
Prednisone/ prednisolone	Initial 20 mg qd Follow up 5-10 mg qd to qod	Diabetes Hypertension Weight gain Osteoporosis Cataracts Glaucoma Moodiness	Bone density Blood pressure and serum glucose	Cumulative toxicity
Methotrexate	10-15 mg once a week	Nausea Leukopenia Hepatotoxicity Pulmonary	CBC, hepatic, renal serum testing	Cleared by kidney, avoid in significant renal failure
Leflunomide	10-20 mg qd	Nausea Leukopenia Hepatotoxicity Pulmonary	CBC, hepatic, renal serum testing	Cleared by kidney, avoid in significant renal failure
Azathioprine	50-250 mg qd	Nausea Leukopenia Infections Malignancy	CBC	
Mycophenolate mofetil	500-1500 mg bid	Diarrhea Leukopenia Infections Malignancy	CBC	Less experience in sarcoidosis than other agents

Infliximab or biosimilars *	3-5 mg/kg initially, 2 weeks later, than once every 4-6 weeks	Infections Allergic reaction	Screen for prior tuberculosis Monitor for allergic reactions Contraindicated in severe CHF, prior malignancy, demyelinating neurologic disease, active tuberculosis, deep fungal infections	Allergic reactions can be life threatening
Adalimumab *	40 mg every 1-2 weeks	Infections	Screen for prior tuberculosis Monitor for allergic reactions Contraindicated in severe CHF, prior malignancy, demyelinating neurologic disease, active tuberculosis, deep fungal infections	Less toxic than infliximab
Rituximab *	500-1000 mg every 1-6 months	Infections	Screen for viral hepatitis Check IgG level with chronic therapy	High risk for viral reactivation Can lead to IgG deficiency
Repository corticotropin injection *	40-80 units twice a week	Diabetes Hypertension Edema Anxiety	Monitor glucose and blood pressure	Most of toxicity is on day of injection
Hydroxychloroquine	200-400 mg qd	Loss of vision	Ocular exams periodically depending on age	Minimal impact on cardiac and

			and renal function	neurologic disease

More details regarding dosage, major toxicity, and monitoring are made in Supplement 1 and adapted from prior reports [4;40-49].

*Use reserved for patients who have failed prior treatments with steroids and/or anti-metabolites.

CBC: complete blood count; qd: daily; bid: twice a day; IgG; immunoglobulin G.

C. **Methodology**

This guideline was developed by an ERS task force chaired by R. Baughman (US) and D. Valeyre (France). The task force included specialists with recognized expertise in the management of patients with sarcoidosis (13 pulmonologists and 1 hematologist/oncologist), three ERS methodologists (T. Tonia, B. Nagavci, and D. Rigau) and three clinician-methodologist (D. Ouellette, P. Korsten, and A. Mathioudakis, 2 general pulmonologists and 1 rheumatologist (PK), who also specialized in sarcoidosis), and three patient representatives from Germany, Italy, and USA.

The guideline panel held four meetings beginning in early 2017. A total of eight clinical questions were formulated using the PICO format (Patients, Intervention, Comparison, Outcomes). Panel members rated selected outcomes as being not important, important, or critical for decision-making (**Table 3**). These outcomes were used as markers for indications for treatment for individual PICOs. Systematic literature reviews (SLR) were conducted for each question. Teams consisting of two sarcoidosis experts, one methodologist, and one patient representative were assigned to each clinical question. Teams met virtually and during physical meetings to address the topics. The patient representatives were full members of the guideline committee and represented three different countries' support groups: Germany, Italy, and United States of America. In addition, we had performed (and published) a large multilanguage questionnaire in which over 1800 sarcoidosis patients rated the level of importance of key outcomes [18].

Table 3

Outcomes for patient care and clinical research

	Measure	Category	Level
Pulmonary sarcoidosis	Patient well-being	Physician judgement	Important
	Clinical judgement of improvement, worsening / progression	Physician judgement	Critical
	Clinical judgement alone		
	Rx chest imaging: Scadding score [20], changes in	RX imaging	Important
	Rx chest imaging: Muers score [50], changes in		
	PET/CT chest imaging, changes in	Scan	Important
	Pulmonary function tests (FVC)	Lung function tests	Critical
	Pulmonary function tests (FEV1)		
	Pulmonary function tests (FEV1/FVC)		
	Pulmonary function tests (DLCO)		
	Pulmonary function tests (SaO2)		
	6MWD [51]	Exercise capacity	Important
	QoL	Quality of life	Important
	SGRQ [52]		
	SF-36 [53]		
	FAS [54]		
	SAT lung [55]		
	KSQ General health [56]		
	KSQ lung health		
	Serious AE; life-threatening AE	Adverse events	Critical
	AE leading to discontinuation		
	Other AE		
Extra-pulmonary sarcoidosis	Physician global assessment (PGA)	Cutaneous sarcoidosis disease activity	Important
	SASI [57]		
	CSAMI [58]		
	Photographs		
	Clinical judgement of improvement, worsening / progression	Physician judgement	Critical
	Skin measure of disease		Important
	Eye measure of disease		Critical
	Kidney measure of disease		Important
	Lofgren syndrome measure of disease		Important
	Hypercalcemia		Critical

	QoL		Critical
	FAS		
	SAT skin [55]		
	SAT fatigue [55]		
	KSQ Dermatology Questionnaire	Quality of life	
	Serious AE; life-threatening AE		Critical
	AE leading to discontinuation		
	Other AE	Adverse events	
Cardiac sarcoidosis	Clinical judgement of improvement, worsening / progression		Critical
	PET/CT chest imaging, changes in		Critical
	MRI chest imaging, changes in		Critical
	Arrythmias		Critical
	QoL		Important
	Serious AE; life-threatening AE		Critical
	AE leading to discontinuation		
	Other AE	Adverse events	
Neuro sarcoidosis	Measures of neurologic disease		Critical
	Clinical judgement of improvement, worsening / progression		Critical
	QoL		Critical
	Serious AE; life-threatening AE		Critical
	AE leading to discontinuation		
	Other AE	Adverse events	
All categories	Steroid sparing	Steroid sparing	Critical

Abbreviations: 6MWD: six minute walk distance; AE: adverse events; CSAMI: cutaneous sarcoidosis activity and morphology instrument; CT: computed tomography; DLCO: diffusing capacity for carbon monoxide; FAS: fatigue assessment scale; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; KSQ: King's sarcoidosis questionnaire; MRI: magnetic resonance imaging; QoL: quality of life; Rx: treatment; PET: positron emission tomography; SaO2: saturation of oxygen; SASI: sarcoidosis activity and severity instrument; SAT: sarcoidosis assessment tool; SF-36: short form 36; SGRQ: Saint George respiratory questionnaire.

Disclosure of potential conflicts of interest: Committee members disclosed all potential conflicts of interest according to ERS policy. Conflicted members were asked to abstain from discussions and voting on recommendations in which they were considered to have potential conflicts. Compliance with the conflict of interest policy was monitored by the chairs. All members, to include the methodologists and the patient representatives, were active voting members of the panel.

Literature searches and systematic literature review: A team of three librarians at an independent center (Henry Ford Hospital, Detroit Michigan, USA) contributed to the development of the systematic review. Searches were conducted in Medline, Embase, and the Cochrane Database of Systematic Reviews between February and July of 2017. An update of the search was performed in November 2018. Furthermore, supplementary searches were conducted (on Pubmed), using relevant studies and systematic reviews to find additional potentially relevant studies not covered by the main searches (latest search: January 2021).

Librarians collaborated with a clinician-methodologist liaison (D. Oullette) to design and run a search strategy using MeSH terms and keywords for each clinical question. The search was limited to studies in the English language. The search retrieved 6968 records. The search was reviewed by sarcoidosis experts for completeness. Teams excluded studies based on pre-defined selection criteria. Some studies required to obtain the full text for review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [59] for each PICO are shown in Supplement S2. We selected randomized controlled trials, and in their absence comparative observational studies, addressing each of the PICO questions. We extracted details on the design, eligibility criteria and interventions of all included studies, on the baseline characteristics of the study participants and on the outcomes of interest. Risk of bias of

randomized controlled trials and observational studies was evaluated using the Cochrane tool risk of bias tool [60] and Newcastle-Ottawa scale [61], respectively. When it was meaningful, meta-analysis was conducted following methodology suggested by Cochrane [62] and the GRADE collaboration [63]. Heterogeneity was assessed using I^2 and meta-analyses were conducted using a random-effects model in anticipation of clinical and methodological heterogeneity [62]. Publication bias was not evaluated as none of the meta-analyses included an adequate number of studies [62]. Certainty in the body of evidence was assessed using GRADE methodology [63]. The PRISMA figures specify the primary articles for each PICO. The evidence summaries, evidence to decision tables, and summary of judgements are shown for each recommendation in Supplement S2. In cases of uncertainty decisions were reached by discussion with the ERS methodologists and consensus. Included references are listed in the evidence summaries.

Assessment of the level of evidence and degree of recommendations: We followed the GRADE approach to assess the confidence in the evidence (quality) and the degree of recommendations [64] . Recommendations were graded as strong or conditional after considering the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the relative importance of outcomes, the implications for resource use, and the acceptability and feasibility of implementation [64]. Evidence summary of findings tables and evidence to decisions frameworks were generated for each clinical question (**Supplementary S2**) [65]. The panel formulated the clinical recommendations and decided on their strength first by consensus and then by voting for final recommendations. Following the GRADE approach, strong recommendations were worded as “we recommend”, while conditional recommendations were worded as “we suggest”.

A strong recommendation was made for an intervention when the panel was certain that the desirable consequences of the intervention outweighed the undesirable consequences, and a strong recommendation against an intervention was made when the opposite was true. A strong recommendation indicates that most patients and health care providers would choose to have, or not to have, the intervention.

A conditional recommendation for an intervention was made when the panel was uncertain that the desirable consequences of an intervention outweighed the undesirable consequences in most patients, and a conditional recommendation against an intervention was made when uncertainty existed that undesirable consequences of an intervention outweighed the desirable consequences in most patients. Reasons for uncertainty included low quality of evidence, a close balance between desirable and undesirable effects, or patients' values and preferences. A conditional recommendation indicates that different patients and health care providers may make different choices regarding an intervention.

In addition to the recommendations, specific considerations were made regarding individual PICOs. These considerations reflect the TF members current practice and describe their clinical experience. They are used in these guidelines to compliment the algorithms, but they are not intended as recommendations for clinical practice. Data supporting these comments was provided for each of the PICOs. For each PICO group, an algorithm was generated and a color code used to differentiate strong (blue) and conditional (orange) recommendations and no color for current practice. In addition, we have added comments regarding continuation of therapy (green) or consider changing therapy (yellow). All recommendations, comments, and algorithms were reviewed and approved by the full panel.

Pulmonary sarcoidosis - general considerations

Treatment indications in patients with pulmonary sarcoidosis are the balance of a) the minimization of risk of disability, loss of life due to pulmonary involvement, or loss of QoL; and b) the risk of comorbidities and loss of QoL due to GC and other therapies[66]. Interstitial lung disease (ILD) or pulmonary hypertension (PH) are the main causes of sarcoidosis-related mortality [6;13;67] and represent risks of life-long exercise intolerance. In Japan, where cardiac involvement is more common than rest of world, cardiac sarcoidosis remains a major cause of death [68]. Many patients suffer from unacceptable loss of QoL due to dyspnea, chest pain, cough, and, variably, malaise, fatigue and arthralgia [69]. We draw a major distinction between treatment decisions based on medical expertise for patients with higher risk disease, and those centered on the wishes of the informed patient, implying the choice, dose, duration, and dose alterations of treatment, which are primarily driven by loss of QoL. As noted above, high risk pulmonary sarcoidosis patients include those with reduced FVC, DLCO, moderate to severe pulmonary fibrosis, or precapillary pulmonary hypertension [6;12;13]. In existing placebo-controlled trials, no distinction is made to separate the treatment goals of minimizing danger and maximizing QoL.

At presentation, patients usually undergo pulmonary function tests (PFT) with measurements of forced vital capacity (FVC), forced expiratory volume in one second (FEV-1), and diffusing capacity for carbon monoxide (DLCO), chest radiography (CXR) and, in those with clinically significant pulmonary sarcoidosis, high-resolution chest computed tomography (HRCT) [69]. In some cases, a six-minute walking distance (6MWD) may be reduced because of pulmonary or cardiac disease, muscle involvement, or fatigue [51]. Transthoracic echocardiography may be indicated in patients with chronic exercise intolerance or suspected PH [70]. General treatment goals are to achieve either disease regression or short-term disease

stabilization (when irreversible) with higher dose GC treatment and to identify the minimum longer-term GC dose required for stabilization of sarcoidosis.

Institution of treatment usually relies on both structural and pulmonary function changes. Both, CXR and HRCT, provide static images of structural changes, whereas the hybrid positron emission tomography (PET) provides both, a structural and functional lung assessment. Lung involvement *per se* is not an indication for treatment, but extensive ILD or pulmonary fibrosis confers an increased long-term risk of respiratory failure [6;13;67]. Evolving evidence suggests that PET can aid intervention response assessment [71;72]. High standardized uptake value (SUV) levels are associated with more rapid and better regression of disease after treatments [49;73-75]. Since PET and HRCT are expensive and associated with radiation exposure, they should be considered on a case by case basis. FVC and DLCO, Borg score for dyspnea, and 6MWD may aid in assessing functional changes [76].

PICO 1

In patients with pulmonary sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?

Recommendation: For untreated patients with major involvement from pulmonary sarcoid believed to be at higher risk of future mortality or permanent disability from sarcoidosis, we recommend the introduction of glucocorticoid treatment, to improve and/or preserve FVC and QoL. (Strong recommendation, low quality of evidence).

Summary of evidence: The clinical outcomes identified by the panel included overall response, CXR and pulmonary function changes, and symptoms. Unfortunately, markers for increased morbidity or mortality were not specifically studied in the identified trials. Our systematic review identified 1747 potentially relevant articles; the full text of 36 were reviewed and 19 were selected [29;32;77-88;88-93]. Many of our prespecified outcomes were not evaluated in these trials.

The overall response to oral GC treatment, based on clinical and radiological evaluation of two studies involving 134 patients [77;78], found a larger proportion of patients experiencing clinical improvement (RR 2.44 [1.40-4.25]) in short term follow-up (3-6 months). There was also a trend towards less patients experiencing clinical deterioration (RR 0.38 [0.11-1.31]), in the short term. In three placebo-controlled trials involving 340 patients [77;79;80], radiographic improvements favoured GC treatment (RR: 1.35 [1.11-1.64]) with a lower prevalence of significant radiographic deterioration (RR: 0.39 [0.18-0.87]). Pulmonary function was not significantly impacted for the whole group [77;79;80], but there was a significant pulmonary function improvement for patients with initial lung involvement [79;81]. Asymptomatic patients without radiographic improvement were randomly allocated to receive either glucocorticoids for at least 18 months or glucocorticoids only if clinically worsened. At 5 years the treated group had better functional outcome [82]. It should be stressed that these data may not apply to the sub-group of patients with higher risk disease. Interventions across the entire range of disease severity, including patients with limited or inactive disease, do not provide guidance in this important sub-group. This especially holds true for failure to demonstrate pulmonary function improvement in whole cohorts, including many patients with mild or intrinsically irreversible disease. Specifically, there is no existing controlled evaluation of GC treatment efficacy in preventing pulmonary function decline in severe pulmonary disease.

Data from additional studies: GC treatment clearly has short-term efficacy by improving symptoms and CXR and in achieving regression or prevention of progression in some cases. Currently, there is no suggestion that these effects are attenuated in higher risk disease. Based on two studies, these benefits appear to be short-lived as they do not persist after discontinuation of GC [78;92]. The dose of GC varied, but two studies found no additional benefit for treating pulmonary disease with more than 20 mg of prednisone a day [83;84]. It has been observed that at least half of patients started on GC were still on treatment two years later [29;32;90]. None of the current studies or accumulated clinical experience specifically evaluated higher risk disease or whether stable disease with GC treatment is likely to progress with the same GC dosage. In summary, the data provide a basis for a likely long-term GC treatment benefit in high risk pulmonary sarcoidosis. To date, no data exist concerning mortality balance between benefits from long-term treatment and risks due to treatment-induced comorbidities. This underlines the importance of re-evaluating the need for GC continuation in the longer term in chronic fibrotic pulmonary sarcoidosis unlikely to benefit from prolonged treatment.

Response to treatment for three to six months, if unsustained after treatment cessation [78;85], provides a solid rationale to limit GC use to patients with higher risk disease or unacceptable loss of QoL or combined pulmonary and systemic symptoms.

In three double-blind placebo controlled randomized trials, the addition of inhaled GC (versus placebo) to oral GC did not provide significant benefits regarding symptoms or PFTs [86-88]

Justification of recommendations: Systemic GC administration is associated with an overall response, as judged by a clinician, or based on clinical and radiological evaluation. It is also associated with

radiological improvement. The strong recommendation for GC use in symptomatic pulmonary patients at risk for mortality is based on data summarized in **Supplement S2** and includes several randomized trials [77;78;80-82;92-94]. This strong recommendation was based on the committee's consensus concerning a serious situation warranting treatment.

For patients with worsening QoL from pulmonary disease, we recommend shared decision-making between physicians and patients with a consideration of initial low to medium dose GC treatment (5 to 10 mg a day) [4]and with the dose and duration of maintenance treatment based on the efficacy/side-effects balance.

For patients not felt to be at risk for morbidity or mortality or have no significant impairment of quality of life, the TF usually offers no GC treatment because of the high prevalence of adverse events. **Figure 1** summarizes this approach.

Future research: There is an urgent need for accurate risk stratification in pulmonary sarcoidosis. Unmet needs include optimal pulmonary function thresholds, integrated with disease duration, and risk assessment for progression in higher risk disease. It is uncertain when higher risk disease is best managed with GC monotherapy as opposed to combination therapy with second or third-line agents. The role of PET in rationalizing long-term treatment following initial stabilization of irreversible disease requires exploration in large cohorts.

A database is needed to quantify GC's therapeutic efficacy in patients with unacceptable loss of QoL, to explore the efficacy and adverse effects with the use of low-dose GC treatment, and to evaluate the optimal dose and duration driven by patient choice.

Another area which needs to be better studied includes how high the initial GC dosage should be, how long to stay on that dose, and how to taper.

PICO 2

In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?

Recommendations:

Recommendation 1) For patients with 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, we suggest the addition of methotrexate to improve and/or preserve FVC and QoL. (Conditional recommendation, very low quality of evidence).

Recommendation 2) For patients with 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, we suggest the addition of infliximab to improve and/or preserve FVC and QoL. (Conditional recommendation, low quality of evidence).

***Summary of evidence*:** Studied populations include patients with chronic symptomatic pulmonary sarcoidosis treated with GCs and/or other immunosuppressive agents. The SLR identified 1319 potentially relevant articles; the full text of 41 were reviewed and 6 were selected [95-100]. We identified six drugs with adequate reports: infliximab (INF), golimumab (GOL), ustekinumab (UST), pentoxifylline, cyclosporine (CsA), and methotrexate (MTX). As displayed in the evidence to decision (EtD) table (**Supplement S2**), most of our preselected outcomes were not evaluated in clinical studies or trials. Some randomized controlled interventions were studied in patients receiving GC. INF, compared to prednisone, significantly improved FVC, the primary endpoint in two phase III randomized trials for the treatment of chronic respiratory symptoms. However, absolute FVC changes were small. Secondary endpoints included chest imaging and QoL assessments [96;98].

In one randomized, double blind, placebo-controlled trial, MTX did not demonstrate significant FVC improvement, although allowing a significant prednisone reduction with lower weight gain in the second six months [95]. Other open label prospective and retrospective trials have found MTX steroid-sparing and associated with improved lung function [46;101;102].

No recommendation could be made for cyclosporine, golimumab, or ustekinumab as randomized trials showed no benefit over placebo [97;100]. These drugs should be considered on a case by case basis.

Data from additional studies: Azathioprine (AZA) is as effective as MTX in pulmonary sarcoidosis [46;103]. Leflunomide (LEF) and mycophenolate mofetil (MMF) are also effective [45;104 47]. In a randomized trial, chloroquine was mildly beneficial in pulmonary sarcoidosis [105]. In a retrospective study from one center,

it was less effective than in skin sarcoidosis[106]. Adalimumab was found effective for pulmonary disease in a prospective, open label trial [107] and a small retrospective series [108].

Some studies support the use of rituximab (RTX) [109]. The CLEAR regimen was found effective in a small uncontrolled observational study [110], but a recently reported double blind placebo controlled trial found no difference in response rate compared to placebo [111]. The committee did not feel that current data supported a treatment recommendation for CLEAR. Repository corticotropin injection (RCI) has been found to be steroid sparing in two retrospective [112;113] and one prospective [49] study. However, the drug is currently quite expensive and mechanism of action remains unclear [114]. There is a reported response to a JAK inhibitor (JAKi) and benefits with anti-interleukin (IL)-6 therapy in small retrospective series [115] [116]. These agents are considered by the TF members on a case by case basis when other therapies are ineffective or not tolerated.

***Justification of recommendation**:* The evidence base of the conditional recommendation for MTX in symptomatic pulmonary patients at risk for mortality is summarized in **Supplement 2** and includes a randomized trial [95]. The conditional recommendation for INF in symptomatic chronic pulmonary sarcoidosis not responding to other immunosuppressives including GC, is based on two trials summarized in **Supplement 2** [96;98]. The committee could not make recommendations on other drugs. Data supporting the use of some drugs is provided in Evidence **Table S2**. **Figure 1** summarizes the approach used by most members of committee.

Future research: Additional studies are needed to evaluate the efficacy, safety, and cost efficiency of RTX, RCI, anti-TNF biosimilars, and other immunosuppressive agents. Also the role of anti-fibrotic agents such as nintenanib and pirfinedone need to be further studied [117]. Newer endpoints, including change in PET and QoL, need to be validated.

Figure 1

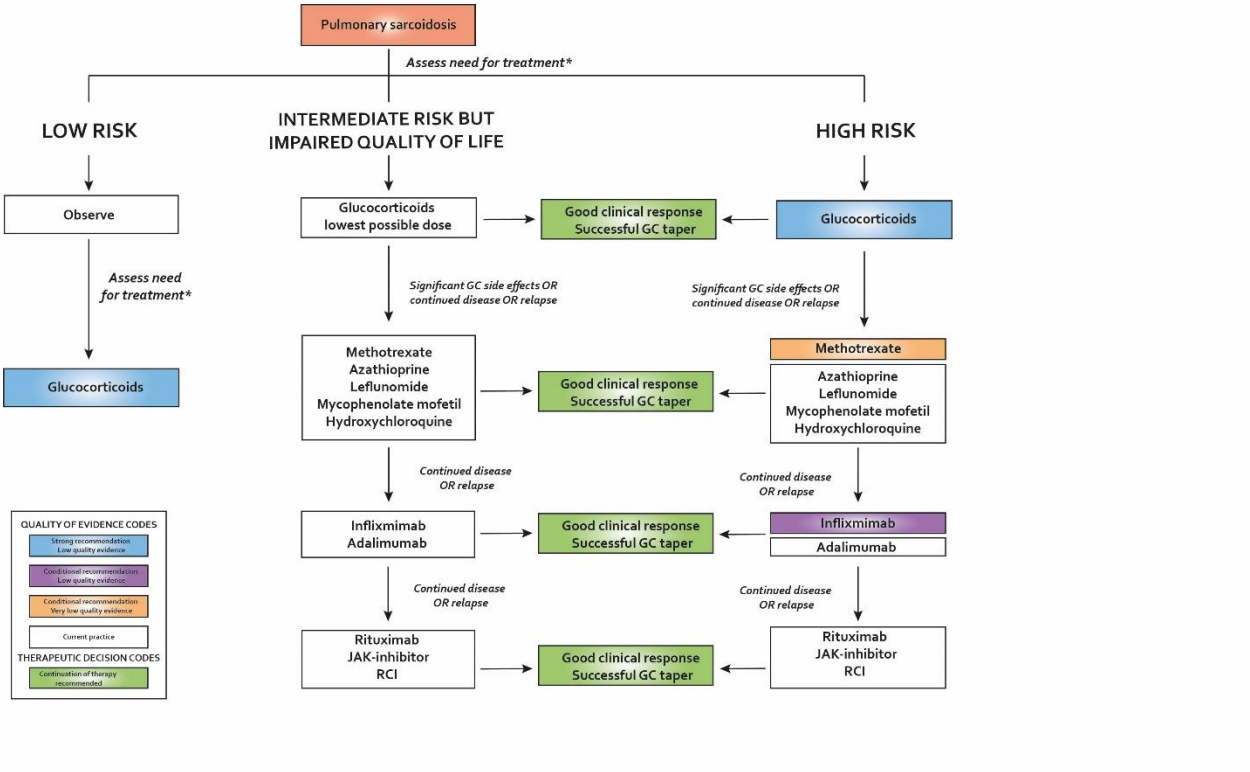

Figure 1: Approach for pulmonary sarcoidosis. Use of rituximab, JAK-inhibitor, and RCI should be on a case by case basis. This figure is a combination of the recommendations made in this guideline, and a description of TF members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white color) is not intended as a recommendation for clinical practice.

GC: glucocorticoids; RCI: repository corticotropin injection.

Cutaneous sarcoidosis - general considerations

Cutaneous sarcoidosis is a rare skin disease but occurs in up to 30% of patients with sarcoidosis, and skin findings are often the initial presenting symptom [118;119]. Skin sarcoidosis can present as a variety of non-specific clinical lesions including papules, plaques, and nodules, but also less commonly as vitiligo, ulcers, alopecia, or subcutaneous nodules [120;121]. Chronic cutaneous sarcoidosis-specific lesions such as lupus pernio can be cosmetically burdensome, occasionally symptomatic, and are difficult to treat [57;122;123]. Treatment of cutaneous sarcoidosis is usually limited to cosmetically important lesions [124]. Therapeutic decisions for cutaneous sarcoidosis are often guided by the impact of disfigurement, the extent of other organ involvement, and are limited by comorbidities that increase the risk of drug toxicity.

Recently, two specific instruments have been used in more than one trial to measure response to treatment. The sarcoidosis activity and severity index (SASI) provides a scale of different aspects of skin disease including erythema, induration, and desquamation [57 58]. Both instruments have been used to assess response to treatments of cutaneous sarcoidosis [123;125-127]. Comparison of paired photographs has also been used [128;129]. The sarcoidosis specific QoL instruments King's Sarcoidosis Health Questionnaire (SHQ) [56] and the Sarcoidosis Assessment Tool (SAT) [55] both contain skin modules and should prove useful in future trials in assess QoL changes with treatment.

PICO 3

In patients with cutaneous sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?

Recommendation:

For patients with cutaneous sarcoidosis and cosmetically important active skin lesions which cannot be controlled by local treatment, we suggest oral glucocorticoids be considered to reduce skin lesions. (Conditional recommendation, very low quality of evidence).

Summary of evidence: This question was originally framed to study patients with extra-pulmonary sarcoidosis treated with GCs versus no treatment. It was narrowed to study patients with cutaneous sarcoidosis when the SLR revealed that this population was the focus of the preponderance of studies in this area. Clinical outcomes identified by the panel as being important included clinical remission and remission of lupus pernio.

Our SLR identified 1032 potentially relevant articles; the full text of 33 were reviewed and 7 were selected [123;130-135]. As seen in our EtD table, most of our preselected outcomes were not evaluated in the trials that we studied. The two outcomes assessed were clinical remission and remission of lupus pernio, as reported by the authors.

There were no randomized trials in this area. We selected 6 retrospective observational cohort studies on skin sarcoidosis with different types of lesions and localizations, all of which studied at least 20 patients [130-135]. Treatment with systemic GC was associated with improvement or remission in up to two thirds of patients. Often, the desired effects were limited to the duration of treatment and recurrences were not uncommon upon GC tapering, requiring additional immunosuppressive therapy. For patients with lupus pernio, a retrospective study on 54 patients showed that only twenty percent of patients

receiving systemic GC alone achieved complete or near complete resolution and fifty percent having some improvement but requiring an average daily prednisone dose of 16 mg [123]. This study employed evaluating photographs of the lesions before and after treatment, but the assessment was retrospective and photographs were obtained at various times during therapy.

Data from additional studies: Topical GC are generally considered to be beneficial for limited skin lesions of mild or moderate extension. However evidence of their efficacy is scarce. In a study of 20 patients who received topical treatment including intralesional administration, only five had complete resolution and the rest had partial resolution [130]. Clobetasol or halobetasol propionate have been used especially for limited and discrete papules and plaque [136;137]. Intralesional injections of triamcinolone acetonide may be more effective than topical preparations [138]. Topical or intralesional GC are impractical for cases with widespread lesions [139].

Justification of recommendation*:* The conditional recommendation for GCs for cosmetically important skin lesions is based on few retrospective studies which reported resolution of lesions. The short-term response was commonly seen. There was insufficient evidence to make a recommendation regarding topical GC. While physicians are comfortable with using GCs, the risk of long-term adverse effects must always be considered.

Implementation consideration: While oral GCs were effective, prolonged use is associated with substantial side effects. Use of steroid-sparing alternatives should be considered whenever possible, especially for chronic lesions such as lupus pernio.

***Future research**:* With the advent of new technologies to assess skin response, the value of topical and systemic GC should be reevaluated. Among the new testing are standardized skin scoring techniques [57;58]. The role of high-frequency ultrasound to assess skin lesions needs further evaluation [140].

Question PICO 4: In patients with cutaneous sarcoidosis, should one add other immunosuppressive treatment when treatment with glucocorticoids has not been effective?

Recommendation:

For patients with cutaneous sarcoidosis who have been treated with glucocorticoids and/or other immunosuppressive agents and have continued cosmetically important active skin disease, we suggest the addition of infliximab compared to no additional treatment to reduce skin lesions (conditional recommendation, low quality of evidence).

Summary of evidence: This question was originally framed to study patients with extra-pulmonary sarcoidosis treated with immunosuppressive treatments compared to those receiving GCs. It was narrowed to study patients with cutaneous sarcoidosis when the SLR revealed that this population was the focus of the preponderance of studies in this area. Clinical outcomes identified by the panel as being important included a validated metric of for assessing cutaneous lesions (the sarcoidosis activity and severity index or SASI score [57;58]) and QoL metrics (SF 36 PCS and SF 36 [141]).

Our SLR identified 980 potentially relevant articles. The full texts of 91 articles were reviewed. We identified five prospective controlled studies of patients with cutaneous sarcoidosis randomized to

either an immunosuppressive agent or continuing GCs that had quantitative data amenable to extraction [97;127;142-144].

We identified two prospective, randomized, controlled studies that compared the use of infliximab to GC to treat cutaneous sarcoidosis and provided data concerning our selected outcomes [127;143]. Baughman and colleagues demonstrated a statistically significant improvement in the SASI desquamation index in patients treated with infliximab compared to GC alone [127]. In an additional study, an extra-pulmonary organ severity tool (ePOST) was used to assess individual organ involvement [143] . The ePOST tool was useful as a broad assessment of each organ, but it was not specific for skin involvement.

Data from additional studies: Two randomized trials using drugs targeted against tumor necrosis factor (TNF) other than infliximab failed to show benefit for treating cutaneous sarcoidosis. One was for golimumab [97] and the other was thalidomide [142]. The latter study used different end points than a previous positive open-label trial of thalidomide for cutaneous sarcoidosis [145]. Adalimumab (also a monoclonal antibody against TNF) has also been studied in one double-blind, placebo-controlled trial and was found to be more effective than placebo for chronic cutaneous sarcoidosis [144]. This study was not abstracted for analysis because only qualitative data was available. Future studies are needed to explore the clinical benefit of adalimumab.

Other treatments have been used for cutaneous sarcoidosis that have not been studied in prospective, randomized, controlled studies. There has been an open-label prospective trials of treatment for

sarcoidosis using chloroquine [146]. The positive response to chloroquine has been confirmed by other case series, many of which included hydroxychloroquine instead of chloroquine [106;130;147]. Methotrexate has been reported as effective in treating cutaneous disease in several series for both adults and children [101;148-150]. There has been an open-label prospective trials of treatment for sarcoidosis with apremilast [125]. The positive response to apremilast study has not been confirmed by either case series or another clinical trial. There have been no clinical series reporting on the use of azathioprine, leflunomide, or mycophenolate mofetil specifically for cutaneous sarcoidosis. These drugs have been reported as useful for chronic sarcoidosis [45-47;104]. However, none of these drugs has specifically studied cutaneous sarcoidosis, so we are unable to make recommendations regarding their use.

We identified one additional study that examined the combination of Levaquin, Ethambutol, Azithromycin, and Rifampin (CLEAR) instead of an immunosuppressive agent and compared this to placebo to treat patients with cutaneous sarcoidosis [126]. Both an intention-to-treat and a per-protocol analysis demonstrated a statistically significant improvement in the SASI score with CLEAR treatment. The CLEAR trial was single-masked study performed at one center and has not been confirmed. However a subsequent larger double blind placebo controlled trial of CLEAR for pulmonary disease found no evidence of effectiveness of this regimen [111]. The committee did not feel that current data supported a treatment recommendation.

Justification of the recommendation: Two small, prospective, randomized, controlled studies demonstrate improvement in sarcoidosis cutaneous lesions as assessed by the SASI score with treatment by infliximab compared to continued GC and other immunosuppressants alone in patients

with cutaneous sarcoidosis [96;127]. Infliximab is an immunomodulatory agent with a risk of adverse effects Including increased susceptibility to infection, though adverse events were low in the analyzed studies. The balance of effects would lead most patients to favor the use of infliximab.

Implementation considerations: Barriers to use of infliximab include the expense of treatment, the availability of facilities for parenteral administration of the agent, and the potential of adverse effects. Some patients might wish to avoid agents that require parenteral administration.

Future research: The skin is an easy organ to assess, resample and biopsy. This makes it a useful target for evaluating new therapies in sarcoidosis. It is important to show whether changes in the skin reflect other organ involvement.

Figure 2

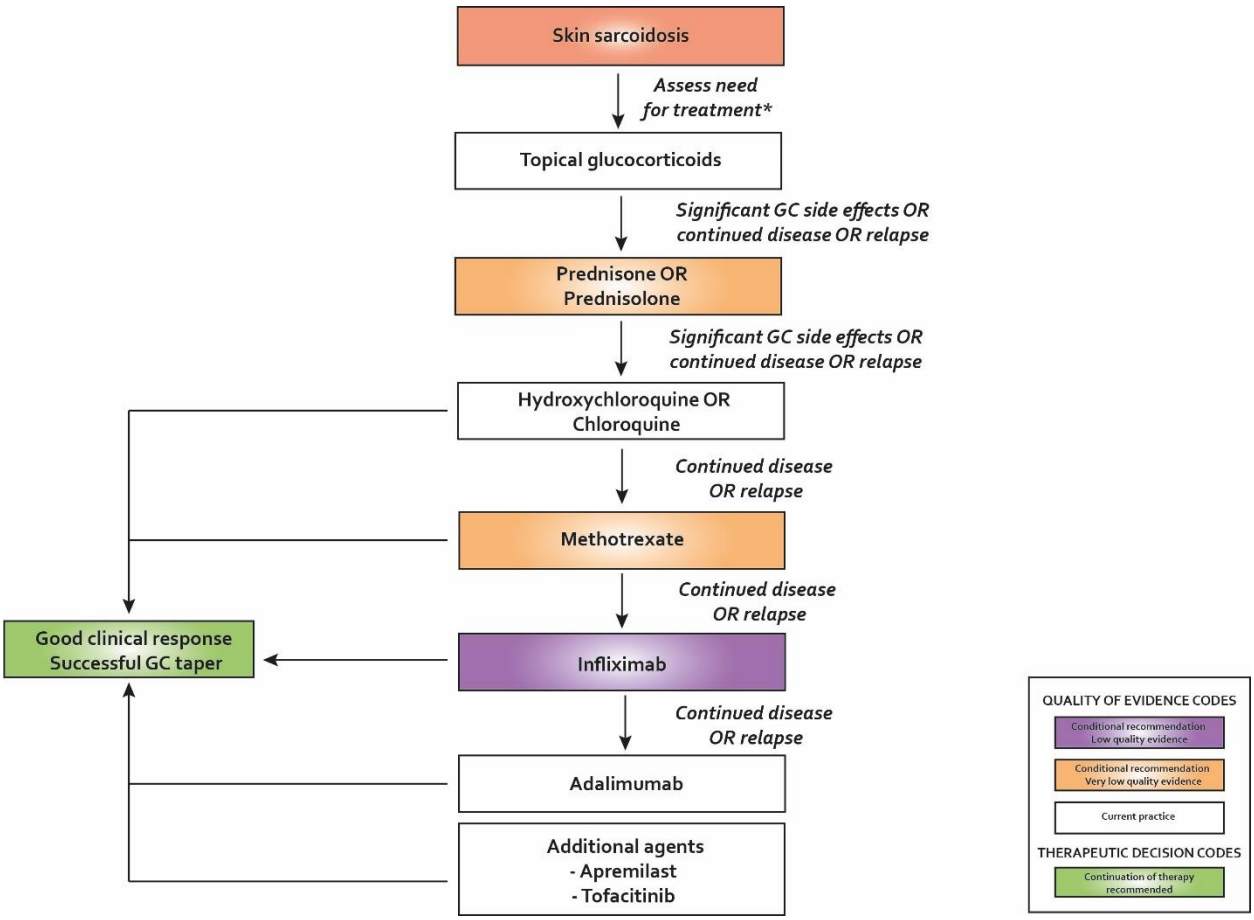

Figure 2: Stepwise approach to management of cosmetically important cutaneous sarcoidosis. Use of apremilast, and tofacitinib should be on a case by case basis. This figure is a combination of the recommendations made in this guideline, and a description of TF members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white color) is not intended as a recommendation for clinical practice.

GC: glucocorticoids

Cardiac sarcoidosis - general considerations

Cardiac involvement is apparent at presentation in 2-5% of unselected patients [151]. However, autopsy studies and the systematic evaluation of patients with chronic sarcoidosis with magnetic resonance imaging (MRI) suggest possible involvement in 25-30% [152;153]. Manifestations of cardiac sarcoidosis include atrioventricular conduction delay, His-Purkinje system conduction block, ventricular and supraventricular tachydysrhythmias, and cardiomyopathy [154]. **Table 4** lists variables that indicate a higher risk for cardiac events in various cohorts and should be considered as factors in the decision about whether or not to treat cardiac sarcoidosis [155;156] [157-164]. Specific recommendations have been made regarding management of cardiac sarcoidosis, mostly in terms of management of arrhythmias [165-167].

Question PICO 5: In patients with clinically relevant cardiac sarcoidosis, should glucocorticoids with or without other immunosuppressives versus no immunosuppression be used?

Recommendation:

For patients with evidence of functional cardiac abnormalities, including heart block, dysrhythmias, or cardiomyopathy, we recommend the use of glucocorticoids (with or without other immunosuppressives) (strong recommendation, very low quality of evidence).

Summary of evidence*:* For this PICO, the clinical outcomes included: improvement, worsening / progression (defined by several findings AND clinical judgement); changes in cardiac PET; changes in cardiac MRI; arrythmias; QoL; and toxicity [160;168-170]. Our SLR identified 996 potentially relevant articles; the full text of 33 were reviewed and 17 were selected [68;155;158;160;162;163;171-181]. The data included

retrospective studies specifically examining the effect of GC treatment versus no treatment and association studies that included GC therapy as a covariate predictor of various cardiac outcomes. No study that specifically assessed the effects of GC therapy enrolled patients prospectively or systematically with sufficient rigor to directly compare the outcomes; all studies were subject to substantial risk of channeling bias or other unmeasured confounders. However, the available data suggest that the risks of important composite cardiac endpoints were reduced, with hazard ratios ranging from 0.33 to 0.78. Many of the endpoint events were driven by appropriate defibrillator or antiarrhythmic therapies, which were inferred (but not proven) to be equivalent to the prevention of sudden cardiac death. Nonetheless, the bulk of the studies evaluated outcomes deemed likely to be of critical importance to affected patients.

Data from additional studies: Heart block is often an early sign of cardiac involvement and it may be the manifestation with the best chance of responding to GC [172;182]. The optimal dose and duration of immunosuppressive therapy are unknown. A retrospective analysis suggested that prednisolone doses higher than 0.5 mg/kg were no more effective than a starting dose of 0.5 mg/kg [183]. It is likewise unclear whether pulse intravenous methylprednisolone is useful and for whom should it be considered [184]. Some data suggest that earlier initiation of GC confers better cardiac outcomes [170]. Similarly, one retrospective case-control study found that withdrawal of GC after initiation of treatment, regardless of clinical improvement, was associated with worse outcomes [185].

Glucocorticoids may lead to significant morbidity [186]; therefore, early initiation of steroid-sparing medications should be considered [69]. However, for cardiac sarcoidosis, the evidence to support steroid-sparing medications is poor, and subject to all the biases described above. The most-commonly

described steroid-sparing agents were methotrexate, azathioprine, mycophenolate mofetil, leflunomide, and cyclophosphamide [159;160;187]. In most of the studies, the patients treated with steroid-sparing agents had no better outcomes that those treated with GC monotherapy, but a single center retrospective study comparing addition of methotrexate to prednisone vs prednisone alone suggested improved ejection fraction and BNP after five years of treatment [169]. Anti-TNF antibodies may be useful for refractory disease [188;189].

Justification of the recommendation:

The level of evidence to support treatment approaches for cardiac sarcoidosis was very low, with multiple potential confounders and biases inherent in the available studies [154;190]. Much of the data supporting the use of GC is indirect, originating in association studies where GC treatment is a covariate among other outcome predictors [190]. There is likewise minimal description in the available studies of the indications for GC treatment, or the characteristics of the treated vs. untreated patients. The risk of death from cardiac sarcoidosis is high, especially for those with reduced left ventricular function [158]. Since GC treatment has been associated with improvement in left ventricular ejection [160;170], the TF members concluded that the danger associated with cardiac sarcoidosis favored GC treatment for clinically relevant cardiac sarcoidosis [21;191]. There was insufficient evidence to make a recommendation regarding other immunosuppressants, but the TF members still consider such treatment to minimize toxicity of GC. **Figure 3** summarizes the approach used by most TF members.

***Future Research*:** An area of current uncertainty is the management of asymptomatic patients with concerning imaging features, such as late gadolinium enhancement (LGE), fluorodeoxyglucose (FDG)

uptake, T2 prolongation or impaired global longitudinal strain, even when cardiac function is preserved and electrical abnormalities are absent [168;192].

Other issues include the optimal dose of GC, duration of treatment, and the role of steroid-sparing medications. There is an urgent need to develop and validate reliable biomarkers and imaging features for the assessment of treatment response.

Table 4

Prognostic variables that may influence treatment decisions for cardiac sarcoidosis

- Age greater than 50
- Left ventricular ejection fraction of less than 40%
- New York Heart Association functional class 3 or 4
- Increased left ventricular end-diastolic diameter
- Late gadolinium enhancement on cardiac MRI
- Ventricular tachycardia
- Cardiac inflammation identified by fluorodeoxyglucose positron emission tomography (FDG-PET) scan
- Echocardiographic evidence of abnormal global longitudinal strain
- Interventricular septal thinning
- Elevated troponin or brain natriuretic peptide (BNP)

Features found to be associated with increased risk for morbidity or mortality from cardiac sarcoidosis [155;156 157-164].

Figure 3

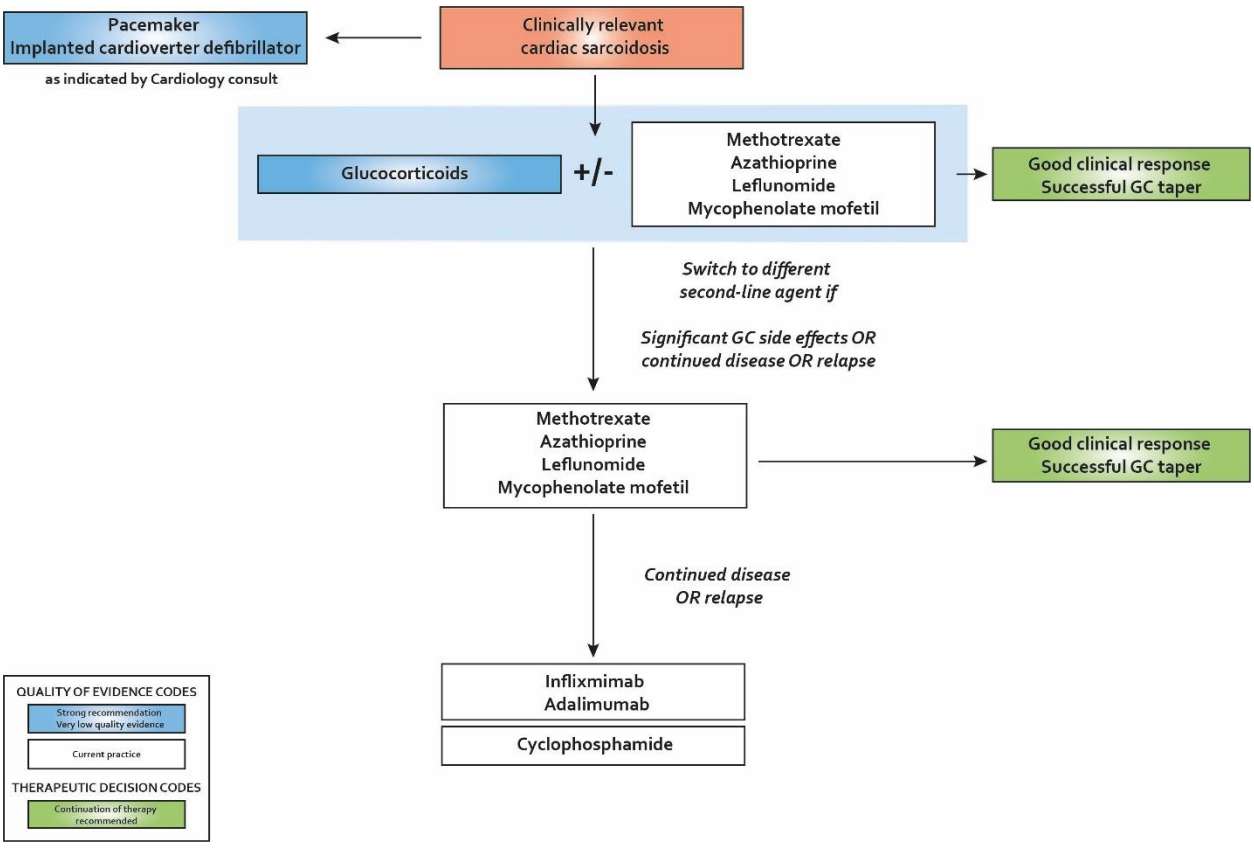

Figure 3: Approach to cardiac sarcoidosis. Use of implanted cardioverter defibrillator recommendation adapted from International Heart Rhythm society [165;167]. This figure is a combination of the recommendations made in this guideline, and a description of TF members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white color) is not intended as a recommendation for clinical practice...

* Clinically relevant cardiac sarcoidosis is defined as rhythm disturbances, heart failure, or high-risk for sudden cardiac death.

Infliximab and adalimumab are usually used in combination with second-line agent.

GC: glucocorticoids.

Neurologic Disease - general considerations

Sarcoidosis can affect any portion of the nervous system. Symptomatic neurosarcoidosis occurs in 5 to 20% of sarcoidosis patients [151;193;194]. Although most sarcoidosis deaths are from pulmonary disease, neurosarcoidosis is an important cause death, and deaths from neurosarcoidosis occur at a younger age [195-197]. Neurosarcoidosis may affect the cranial nerves, brain, leptomeninges, and peripheral nerves. The clinical manifestations of symptomatic neurosarcoidosis often have a significant deleterious impact of the sarcoidosis patient's QoL, and include facial nerve palsy, optic neuritis, aseptic meningitis, serious sequelae from central nervous system granulomatous mass lesions, hydrocephalus, and encephalopathy/psychosis [196;198].

Question PICO 6: ***In patients with neurosarcoidosis, should immunosuppressive treatment be used versus no immunosuppressive treatment?***

Recommendations

Recommendation 1) For patients with clinically significant neurosarcoidosis, we recommend treatment with glucocorticoids (Strong recommendation, very low quality of evidence).

Recommendation 2) For patients with neurosarcoidosis that have been treated with glucocorticoids and have continued disease, we suggest the addition of methotrexate (conditional recommendation, very low quality of evidence).

Recommendation 3) For patients with neurosarcoidosis that have been treated with glucocorticoids and a second-line agent (methotrexate, azathioprine, mycophenolate mofetil) and have continued disease, we suggest the addition of infliximab (conditional recommendation, very low quality of evidence).

Summary of evidence: The clinical outcomes that were evaluated were: improvement, worsening / progression (defined by several findings AND clinical judgement); QoL; and toxicity. Our SLR identified 1305 potentially relevant articles; the full text of 56 were reviewed and 4 were selected [36;196;199;200].

One retrospective analysis of 234 neurosarcoidosis patients [196] found that although treatment with GC alone significantly lowered the overall relapse rate of sarcoidosis compared to no treatment (hazard ratio 0.59; 0.39 – 0.90; p=0.01), the specific rate of neurosarcoidosis relapse was not significantly affected (hazard ratio 0.68; 0.38 – 1.23; p=0.2). Additional drugs besides GCs were found to significantly lower the relapse rate of neurosarcoidosis in this cohort (vide infra), and most of these drugs were used in combination with GC; this suggests GC may have contributed to protecting against neurosarcoidosis relapse in these cases. In a meta-analysis of 1088 neurosarcoidosis patients [199], GC were initiated as first-line therapy in 434 of 539 (81%) treated patients, and a favorable outcome was reported in 161 out of 227 (71%, confidence interval: 65%-77%) patients who only received GC. We believe that these data, although limited, support the use of GC as first-line therapy for neurosarcoidosis.

Joubert and colleagues [196] demonstrated that infliximab statistically significantly lowered the rate of overall sarcoidosis relapse (hazard ratio 0.31; 0.11 – 0.82; p=0.02) but failed to demonstrate a statistically significant lower relapse rate of neurosarcoidosis (hazard ratio 0.16; 0.02 – 1.24; p>0.05). A retrospective report demonstrated good neuroimaging and functional outcomes in 66 neurosarcoidosis patients treated with infliximab-containing regimens [36].

Data from additional studies: Reports of treatment of neurosarcoidosis consist of the second-line agents methotrexate, azathioprine, and mycophenolate mofetil as well as anti-malarial drugs and cyclosposporin A. These drugs are usually added to GC treatment when GCs are ineffective or a relapse occurs after tapering. These drugs may be used concomitantly with GC as part of the initial treatment of neurosarcoidosis. The evidence for these agents is also sparse, with the possible exception of methotrexate [201]. An analysis from one institution [196] found a statistically significant reduction in the relapse rate of neurosarcoidosis with methotrexate (MTX) (hazard ratio 0.47; 0.25 – 0.87; p=0.02), and hydroxychloroquine (hazard ratio 0.37; 0.15 – 0.92; p=0.03), but not with azathioprine (hazard ratio 1.88; 0.69 – 5.14; p=0.22), or mycophenolate mofetil (hazard ratio 0.58; 0.25 – 1.34; p = 0.20). In the previously described meta-analysis [199], treatment with MTX, azathioprine, hydroxychloroquine, was initiated in 144 of the 539 (27%) patients who were treated for neurosarcoidosis. A favorable outcome was observed in 47 of the 85 (55%, confidence interval: 45%-66%) patients who received these agents and were not switched to third-line therapy. A retrospective analysis was performed concerning 40 neurosarcoidosis patients who received either MTX (n=32) and/or mycophenolate mofetil (n=14) as part of their treatment regimen [200]. Those who received MTX had a significantly lower yearly relapse rate than those who received mycophenolate mofetil (0.2 relapses/year vs. 0.6 relapses/year, p = 0.058) and the median time to relapse was also longer in the MTX group (28 months vs. 11 months, p = 0.049). To summarize the available data concerning the use of non biologic agents for the treatment of

neurosarcoidosis, the limited data support the use of MTX. Although the evidence for the other agents is minimal, there is inadequate evidence to state that these agents are ineffective for neurosarcoidosis. After MTX, we would consider azathioprine, mycophenolate mofetil, or hydroxychloroquine. Although chloroquine and cyclosporine A could also be considered as potential second-line agents for neurosarcoidosis, their side effect profile suggests that other non biologic agents should be preferred. We are only aware of two case reports suggesting that adalimumab is beneficial for the treatment of neurosarcoidosis [202;203]. There is low-quality evidence supporting cyclophosphamide for the treatment of neurosarcoidosis. In one study [196], intravenous cyclophosphamide statistically significantly lowered the rate of relapse of neurosarcoidosis compared to untreated patients (hazard ratio 0.26; 0.11 – 0.59; p=0.001). In addition, in a retrospective series [201;204], cyclophosphamide was found to be beneficial for neurosarcoidosis that was refractory to GCs and MTX. Despite the potential efficacy of cyclophosphamide for the treatment of neurosarcoidosis, we believe that infliximab and even adalimumab are more preferred based on the side effect profiles of these agents.

***Justification of recommendation**:* The strong recommendation for GCs for clinically significant neurosarcoidosis is based on very low quality of evidence, the committee felt the high risk for significant irreversible neurologic loss warranted the strong recommendation. The conditional recommendation for infliximab was based on two retrospective studies [36;205] and other studies, as summarized in **Supplement S2**.

Clinical evidence concerning the treatment of neurosarcoidosis is meager due to the absence of any RCT and to the wide variety of outcomes evaluated in retrospective studies (neuroimaging, remission/relapse, functional status, mortality) which evaluated different drugs. In addition, because drugs trials for neurosarcoidosis have not rigorously compared specific agents against other ones, our

recommendations concerning the step-wise approach to the treatment of neurosarcoidosis are based not only on efficacy data but also drug cost, side effect profile, and ease of use. **Figure 4** shows the committees usual approach to treating neurosarcoidosis.

Future research Studies confirming effectiveness of infliximab for neurosarcoidosis need to be performed. Studies examining whether high-dose GCs are required with infliximab as initial treatment for advanced neurosarcoidosis may help reduce the burden of GC toxicity. These studies would require standardized outcome measures. Given the relative rarity of neurosarcoidosis, multicenter studies will most likely be required. In addition, neurosarcoidosis may not be amenable to uniform treatment decisions but may require different treatments depending both on the localization and the severity of affection (central, peripheral, spine).

Figure 4

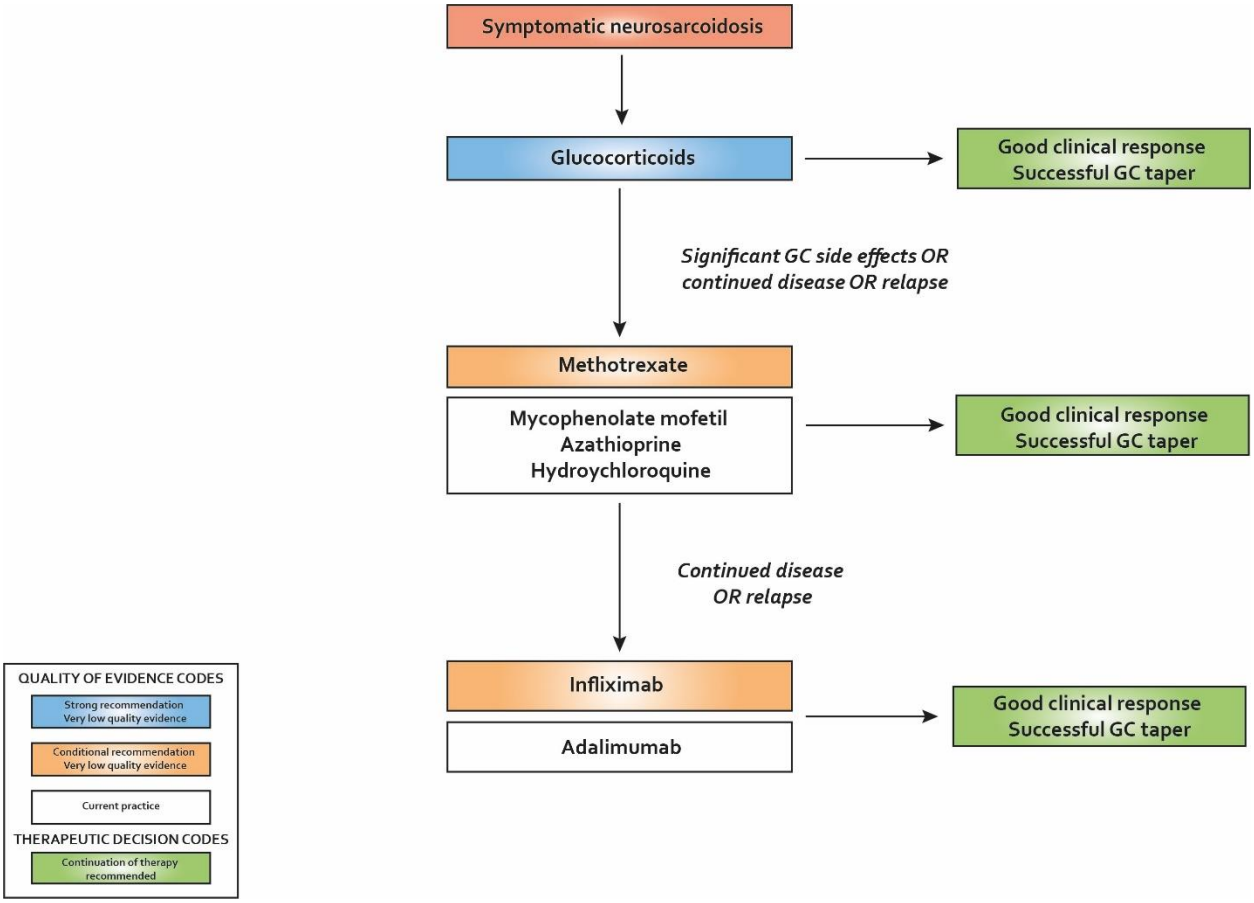

Figure 4: Approach to neurologic sarcoidosis. This figure is a combination of the recommendations made in this guideline, and a description of TF members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white color) is not intended as a recommendation for clinical practice.

* Infliximab and adalimumab are usually used in combination with second-line agent.

GC: glucocorticoids.

Fatigue - general considerations

Background: Fatigue is a very common symptom in sarcoidosis, reported in up to 90% of patients and is strongly associated with a lower QoL [206;207]. It is not always related to organ involvement induced by sarcoidosis and may persist for many years, even after apparent remission of active granulomatous inflammation [208]. Other causes of fatigue have to be ruled out before sarcoidosis-associated fatigue (SAF) can be diagnosed [15]. These include diabetes mellitus, thyroid dysfunction;, neuroendocrine disorders, mental disorders (esp. depression), obstructive sleep apnea; small fiber neuropathy, vitamin D deficiency (esp. low 1,25-dihydroxycholecalciferol), heart failure, and neurologic disease. Also, studies have shown poor agreement between physicians' and patients' assessment of SAF highlighting the importance of using patient reported outcome measures (PROMs) for the evaluation of effects of interventions in clinical trials and clinical practice [209].

Question PICO 7: In patients with sarcoidosis-associated fatigue, should immunosuppressants, neurostimulants, exercise, or other treatments be used versus no treatment for fatigue?

Recommendation

Recommendation 1) In patients with sarcoidosis who have troublesome fatigue, we suggest a pulmonary rehabilitation program and/or inspiratory muscle strength training for 6-12 weeks to improve fatigue. (Conditional recommendation, low quality of evidence).

Recommendation 2) In patients with sarcoidosis who have troublesome fatigue that is not related to disease activity, and after consideration of a pulmonary exercise or rehabilitation program, we

suggest the use of d-methylphenidate or armodafinil for 8 weeks to tests its effect on fatigue and tolerability (Conditional recommendation, low quality of evidence).

Summary of evidence: Our SLR of articles regarding fatigue and sarcoidosis identified 165 potentially relevant articles; the full text of 27 were reviewed and 5 were selected [210-214] One of these was of an experimental intervention not available at this time (cibinetide) [214]. The remaining four articles were reviewed.

Two of the interventions involved RCTs with physical therapist interventions. Inspiratory muscle training for 6 weeks has been studied, which led to significant improvement of 6MWT, Borg dyspnea scale, maximal inspiratory and expiratory pressure, and fatigue severity scale in the treatment group [215]. A second RCT has tested the effect of a structured exercise program for 12 weeks [212]. Significant effects were found on the following outcomes: 6MWT, Borg dyspnea scale, MMRC, maximal inspiratory force, leg strength, PaO2, and fatigue severity scale and SGRQ.

Pharmacologic interventions with neurostimulants have also been evaluated by two RCTs. Dexmethylphenidate hydrochloride (d-MPH) was given to 10 patients with median Functional Assessment of Chronic Illness Treatment-Fatigue (FACIT-F) score of 16 (range 4-37) and Fatigue Assessment Scale (FAS) of 38 (22-44) in a randomized cross over trial [210]. The improvement in fatigue at 8 weeks for the d-MPH group was 36%, similar to the improvement seen in patients with cancer chemotherapy-related fatigue [216]. In that study, no difference in toxicity was noted between drug and placebo. The other RCT investigated armodafanil 150 mg daily for four weeks, then 250 mg daily for four weeks [211]. This resulted in an improvement in fatigue as measured by the FAS and FACIT-F scores. Only

15 patients were studied. One patient withdrew because of anxiety. The adverse effects of methylphenidate and armodafanil are known from other patient populations and include addiction, insomnia, anxiety, and tachycardia [217].

Data from additional studies: Other observational studies have shown positive effects of exercise training or rehabilitation programs on SAF and other parameters associated with reduced QoL [218-220]. One study demonstrated improvement in fatigue as well as 6MWD for those participating in pulmonary rehabilitation [221]. A recent randomized trial, published since our SLR of the literature, found that rehabilitation improved fatigue [222]. This regimen was comparable to other pharmacologic interventions [223]. A recent RCT showed that the use of low-dose GCs has also been shown to alleviate SAF, especially in the context of ongoing inflammation [224], but the committee felt there was insufficient evidence to make a recommendation regarding low-dose GCs.

Justification of recommendation: The conditional recommendations for the treatment for SAF were each supported by one prospective trial. In the cases of physical treatment intervention, one study used a sham procedure for control, the other had compared patients who chose not to participate in structured training. The pharmacologic interventions were both studied in double-blind, placebo-controlled, crossover design. However, only a limited number of subjects were studied.

Future research: Further research is needed to confirm the effects of inspiratory muscle training, which have been noted in a single study, and to review the impact of the recommendation regarding physical training upon costs, resources, and health care equity. The long-term effects should also be explored, especially how improvement can best be maintained after end of training or a systematic rehabilitation program.

Further research is needed to confirm the effects and toxicity of d-MPH and armodafanil which has been noted in two single-center studies, and to review the impact of the recommendation upon costs, resources, and health care equity. The effects of long-term use of d-MPH and armodafanil should be explored.

Figure 5

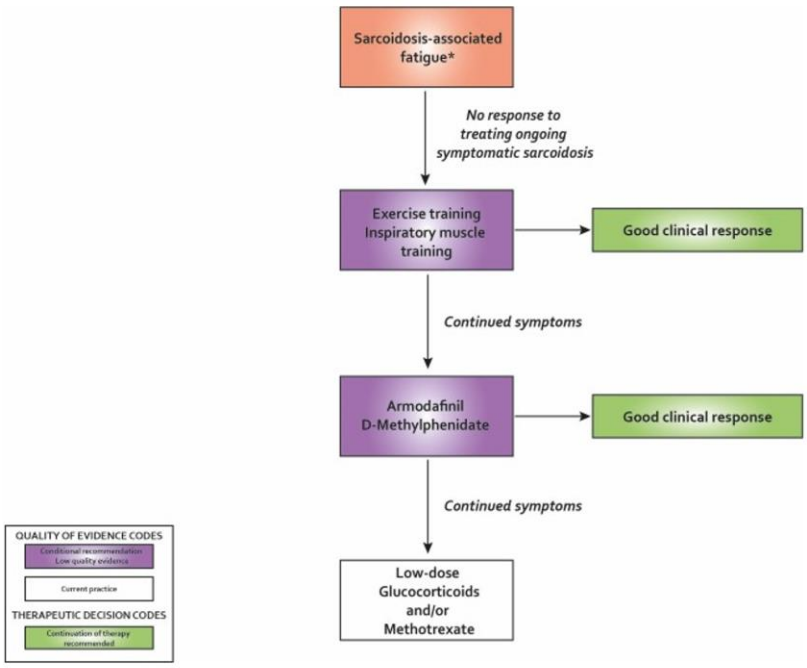

Figure 5. Approach to the evaluation and management of sarcoidosis-associated fatigue. The use of low-dose corticosteroids with or without methotrexate should be considered on a case by case basis. This figure is a combination of the recommendations made in this guideline, and a description of TF members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white color) is not intended as a recommendation for clinical practice.

*Other causes of fatigue include diabetes mellitus, thyroid dysfunction, neuroendocrine disorders, sleep apnea, small-fiber neuropathy, vitamin D deficiency with low 1,25-dihydroxycholecalciferol, congestive heart failure, and neurologic disease.

Small fiber neuropathy - general considerations

Background: Apart from idiopathic cases, small fiber neuropathy (SFN) has been associated with various underlying conditions. SFN is a non-granulomatous disorder characterized by neuropathic symptoms and dysautonomia due to loss of thinly myelinated and unmyelinated nerve fibers. It occurs in approximately 40-60% of sarcoidosis patients, and is more prevalent in Caucasians and females [17;225-229]. Symptoms may include paresthesias, allodynia, numbness, pain syndromes, gastrointestinal dysmotility, diaphoresis, orthostasis, palpitations, and any other symptoms associated with dysautonomia. The small fiber neuropathy screening list (SFNSL) is a validated 21 item self-administered instrument that is useful to screen for the presence of SFN associated symptoms in sarcoidosis patients [16;230]. There is no diagnostic gold standard for diagnosing SFN. The combination of typical symptoms and the absence of large fiber involvement is required. Once suspected, the diagnosis can be confirmed by specialized tests such as skin biopsy for intraepidermal nerve fiber density, nerve fiber density assessed by corneal confocal microscopy, quantitative sudomotor axonal reflex test, and thermal threshold testing [226-229]. Due to lack of awareness among clinical physicians, the diagnosis of SFN is probably highly underreported [16;206]. The treatment for SFN includes agents specific for the condition such as intravenous immunoglobulin (IVIg) and anti-TNF therapy as well as supportive care for neuropathic symptoms [17;231].

Question PICO 8: In sarcoidosis patients with small fiber neuropathy, should immunosuppressants or intravenous immunoglobulin be prescribed versus no treatment?

No recommendations were made for this PICO question due to a lack of sufficient evidence.

Summary of evidence: Our SLR identified 427 potentially relevant articles; the full text of 9 were reviewed and 4 were selected. Three of these involved the cibinetide [214;232;233], an erythropoietin analogue, which is currently not available for clinical use. The other was a large retrospective review from one center evaluating IVIg and/or anti-TNF monoclonal antibody treatment [17]. There are no validated, widely-available endpoints for evaluating the effect of SFN treatment in patients with sarcoidosis [16;225;227]. The clinical outcomes that were evaluated in this analysis were: measures of pain, measures of SFN: QART, skin biopsies, SFN scale, cognitive scale, and confocal microscopy. We were not able to identify sufficient treatment evidence to warrant a recommendation for any commercially available agent.

Data from additional studies: Treatment of SFN depends on the underlying disease, if identified. Symptoms are often disabling and difficult to alleviate, even when the cause is identified and adequately treated, leading to high morbidity and decreased QoL [225]. Usually, only symptomatic relief of complaints can be achieved. Guidelines for neuropathic pain have been adapted from the treatment regimens developed for other causes of SFN related pain [225;228]. There is no consensus regarding evaluating outcome for response to specific therapy for SFN. To date, studies have evaluated improvement in the autonomic symptoms, fiber neuropathy symptoms and the related pain, and the number of small fibers in cornea [214;232;233]. However, these have not been routinely applied and were not employed in retrospective reports [17;234;235].

A large observational study found that that 75% of patients derived symptomatic benefit from a dosing regimen of IV Ig either alone or in conjunction with anti-TNF monoclonal antibody therapy. The dosing regimen was like that described for chronic inflammatory demyelinating polyneuropathy [17]. A total of 79

patients were treated with IVIg alone or with anti-TNF monoclonal antibodies and were evaluated [17;234]. The data are limited by the absence of a defined standard for assessing treatment response, patient selection bias, differences in concomitant treatment regimens, and lack of a placebo group. Thus, conclusions regarding the usefulness of IVIg are preliminary currently. Nonetheless, a significant subset of patients are observed to experience moderate to dramatic improvements in symptoms and functionality within several months of initiating treatment [234]. The putative mechanism for effectiveness of IVIg is unclear, but may relate to immunomodulatory effects [236].

TNF may be a proximate trigger for central and peripheral inflammatory cascades that are postulated to cause neuropathy, as well as sarcoidosis itself [237]. The monocloncal anti-TNF antagonists infliximab and adalimumab have been assessed in two retrospective cohorts totaling 115 patients [17;238]. These reports suggested that SFN-associated symptoms may respond to TNF inhibition, although the magnitude of the effect is difficult to ascertain from the available data. The GG promoter variant, associated with less exuberant TNF transcription, was also associated with better outcomes in treated patients [238].

Cibinetide, previously known as ARA-290, is an innate repair receptor agonist that has anti-inflammatory and neuroprotective properties [239-241]. Cibinetide is not yet approved for any indication, so it is not the subject of a formal recommendation in this document. More importantly, it is not commercially available currently. However, cibinetide is the most extensively studied and best validated treatment to date for sarcoidosis-associated SFN. In three randomized, placebo-controlled, double-blind studies, it has been shown to reduce symptom scores and improve markers of corneal nerve fiber health over short time-frames [214;232;233]. Interestingly, these neuropathic benefits correlated with increases in the 6MWD, underscoring the important functional consequences of SFN [214;233;240].

Justification: There were no studies with suffficient results to support any specific recommendations for SFN due to sarcoidosis. However, we have presented the current practise of managing SFN, summarized in **Figure 6**.

Future research: Safety and clinical effectiveness of cibinetide, IVIg, anti-TNF antibodies, and other interventions for patients with sarcoidosis and SFN needs to be investigated. Development and clinical validation of accurate biomarkers and/or clinical scores to assess treatment response should be developed.

Figure 6

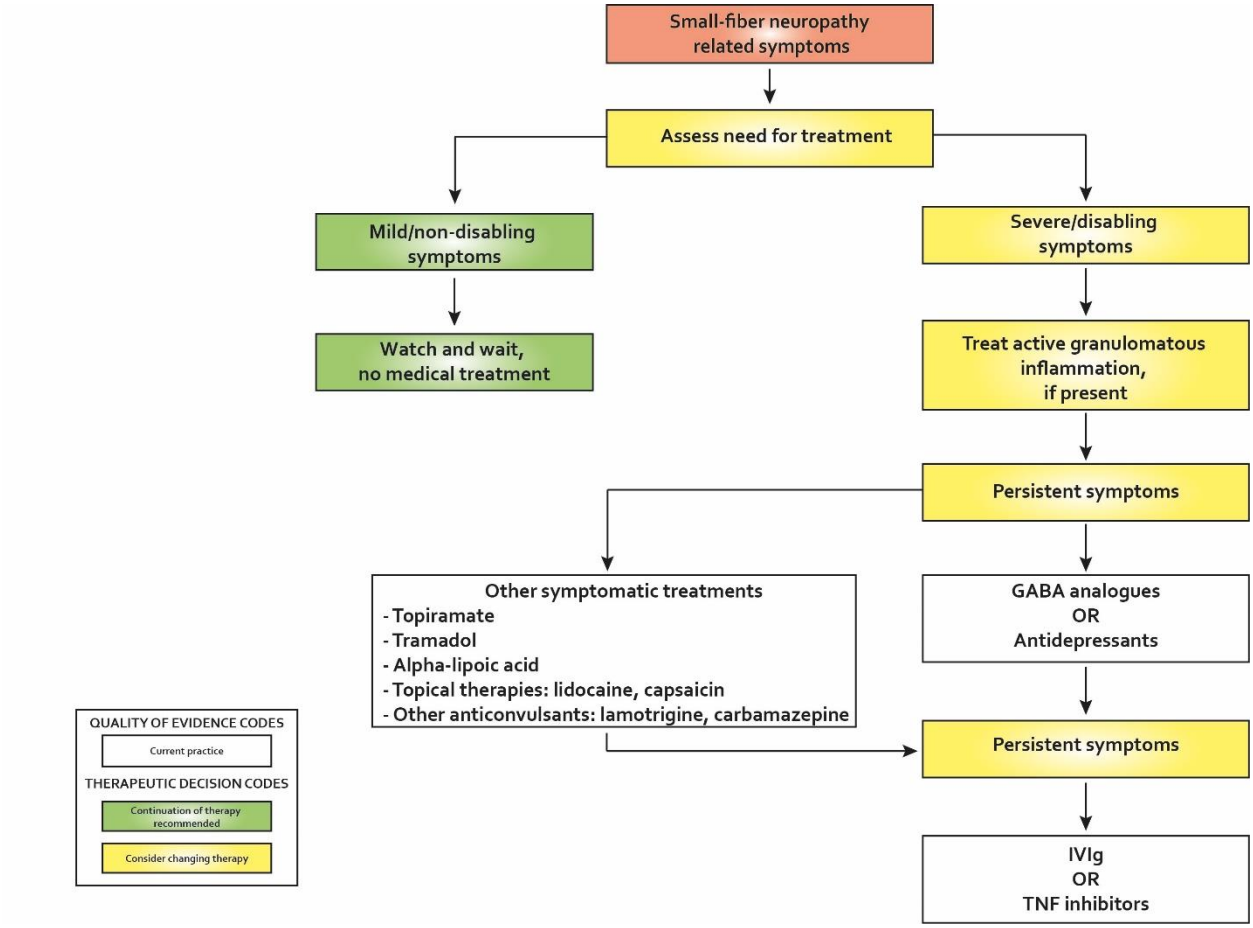

Figure 6: An approach to small fiber neuropathy symptoms used by TF members. The use of intravenous immunoglobulin or anti-TNF antagonists should be considered on a case by case basis. This figure is a combination of the recommendations made in this guideline, and a description of TF members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white color) is not intended as a recommendation for clinical practice.

GABA: Gamma-aminobutyric acid; IVIg: intravenous immunoglobulin; TNF: tumor necrosis factor.

Discussion

The management of sarcoidosis can be challenging. The clinician must remember not to focus on a single manifestation, but to look at the various manifestations both initially and over time [151;242;243]. The outcome of the disease is variable. Some patients have a very good outcome and never require treatment [244]. Less than 10% of patients die, mostly from advanced lung disease [6;13;67]. For many patients, the response to anti-inflammatory treatment can readily be seen. However, recurrence of disease is common if treatment is withdrawn too soon, and at least a quarter of patients require treatment for more than two years [29;31;32]. This treatment guideline concerns mainly "sarcoidosis-modifying treatment" and did not make specific recommendations regarding useful treatments such as oxygen supplementation, implantable cardiac devices, or organ transplantation.

This divergence of outcomes has led to confusion about who should or should not be treated. In this document, we propose that patients be treated either for risk of death and/or permanent disability (danger), or to improve QoL [66;245]. This concept has become readily accepted in clinical practice [69]. However, the evidence for effectiveness of treatment, especially to improve QoL, is relatively weak. Recently, two sarcoidosis specific QoL instruments have been developed [55;56]. The impact of treatment on these instruments has been reported [49;97;246]. However, we still need more information before we can be confident about the impact of treatment on QoL.

The majority of studies regarding treatment of symptomatic sarcoidosis have focused on pulmonary disease [41]. However, several studies have evaluated other manifestations such as skin, heart, and neurologic disease. These non-pulmonary studies were useful in answering several of the PICOs in this report. However, there was insufficient information to evaluate treatment for other extrapulmonary disease such as liver, bone, or eye disease. Symptoms of SAF and SFN are well established [15;228;247], however, most studies in this area have been small and usually from a single center [17;210;211;221;233].

The report has several limitations. All authors felt there was much to do: 1) the indications for treatment remain unclear and mostly based on a case by case basis; 2)measurements of response to treatments are still too heterogeneous; 3) clinical trials may provide more information [141]; 4)single endpoints such as FVC or chest imaging may not be reliable and a composite score evaluating physiology, radiology, QoL, and steroid-sparing may be more effective [248].

In conclusion, we do not feel these guidelines are the final word on management of sarcoidosis. Through a systematic review of literature, the committee identified areas where there is sufficient information to make informed recommendations based on current evidence and our clinical experience. At the same time, areas where research on this topic is lacking or is not sufficient to make recommendations were also identified. We anticipate that an update of this guideline will be needed within the next five years as more information becomes available.

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ERS Task Force Therapy for Sarcoidosis

Supplement 1 Individual therapies

The task force made specific recommendations regarding therapy for various manifestations of sarcoidosis. Most of these recommendations involve anti-inflammatory therapies. In general, the dose and duration of therapy is similar for the different manifestations. In those cases where there are differences, these are usually discussed within the individual PICO.

About half of patients with sarcoidosis are treated with one or more anti-inflammatory therapy (1;2). The prolonged dose of these drugs can lead to significant toxicity. Prednisone is the most commonly employed medication for treating sarcoidosis and has been associated with significant morbidity, especially weight gain (3-6). However, other agents may lead to specific toxicity. Table S-1 summarizes the various anti-inflammatory treatments used for sarcoidosis, including their toxicity.

Table S-1

Anti-inflammatory therapies for sarcoidosis

Drug	Dosage	Major Toxicity	Recommended monitoring	Comments
Prednisone/ prednisolone	Initial 20 mg qd Follow up 5-10 mg qd to qod	Diabetes Hypertension Weight gain Osteoporosis Cataracts Glaucoma Moodiness	Bone density Blood pressure and serum glucose	Cumulative toxicity
Methotrexate	10-15 mg once a week	Nausea Leukopenia Hepatotoxicity Pulmonary	CBC, hepatic, renal serum testing	Cleared by kidney, avoid in significant renal failure
Leflunomide	10-20 mg qd	Nausea Leukopenia Hepatotoxicity Pulmonary	CBC, hepatic, renal serum testing	Cleared by kidney, avoid in significant renal failure
Azathioprine	50-250 mg qd	Nausea Leukopenia Infections Malignancy	CBC	
Mycophenolate	500-1500 mg bid	Diarrhea Leukopenia Infections	CBC	Less experience in sarcoidosis than other agents

		Malignancy		
Infliximab or biosimilars *	3-5 mg/kg initially, 2 weeks later, than once every 4-6 weeks	Infections Allergic reaction	Screen for prior tuberculosis Monitor for allergic reactions Contraindicated in severe CHF, prior malignancy, demyelinating neurologic disease, active tuberculosis, deep fungal infections	Allergic reactions can be life threatening
Adalimumab *	40 mg every 1-2 weeks	Infections	Screen for prior tuberculosis Monitor for allergic reactions Contraindicated in severe CHF, prior malignancy, demyelinating neurologic disease, active tuberculosis, deep fungal infections	Less toxic than infliximab
Rituximab *	500-1000 mg every 1-6 months	Infections	Screen for viral hepatitis Check IgG level with chronic therapy	High risk for viral reactivation Can lead to IgG deficiency
Repository corticotropin injection *	40-80 units twice a week	Diabetes Hypertension Edema Anxiety	Monitor glucose and blood pressure	Most of toxicity is on day of injection
Hydroxychloroquine	200-400 mg qd	Loss of vision	Ocular exams every	Minimal impact

			6-12 months	on cardiac and neurologic disease

*Used reserved for patients who have failed prior treatments with steroids and/or anti-metabolites.
CBC: complete blood count; qd: daily; bid: twice a day; IgG; immunoglobin G;
Adapted from Obi O and Baughman RP.

Glucocorticoids: Prednisone and prednisolone are the two most commonly used drugs of this class, although hydrocortisone and dexamethasone have also been used. These drugs were approved for treatment in the 1950s based on reports of the utility of glucocorticoids and adrenal cortisol stimulating hormone (ACTH) (7;8). The dose of prednisone is unclear (9). Initial studies often gave 1 mg per kilogram body weight or an absolute dose of 40 mg a day. In a multi-center observational study, Broos et al observed that the response as assessed by improvement in FVC was not related to the dose of prednisone (5). In a retrospective study of sarcoidosis patients treated for worsening pulmonary symptoms, McKinzie et al found that 20 mg a day was as effective as higher doses in improving FVC (10). In cardiac sarcoidosis, a retrospective analysis found no benefit for giving more than 30 mg a day of prednisone (11). Prolonged prednisone therapy is associated with significant toxicity (12), including weight gain (5;13), diabetes, mood swings, osteoporosis, and cataracts (3). Therefore alternative agents which are steroid sparing have been investigated.

Methotrexate: Of the second line agents for pulmonary sarcoidosis, methotrexate has been the most widely studied. Original reports indicated that approximately two thirds of patients were able to reduce or stop prednisone use after six months of therapy (14;15). Subsequent other studies confirmed the effectiveness of methotrexate (16-18). Guidelines regarding dosage and monitoring sarcoidosis patients have been established (19).

Leflunomide is similar to methotrexate in action but with a different toxicity profile. It has been reported as effective in sarcoidosis as an alternative to methotrexate (20;21) and in some case has been used in combination with methotrexate (20). It is associated with less nausea and pulmonary toxicity (22). However, it can cause a peripheral neuropathy (23).

Azathioprine is a different anti metabolite which has been used to prevent solid organ rejection. It has been reported as effective as steroid sparing agent, although reported effectiveness ranges from 20 to 80% (17;24-26). Overall, azathioprine has more reported adverse events than methotrexate leading to more frequent withdrawal of the drug (17). The major complications are infections, increased gastrointestinal toxicity, and increased risk for myelodysplasia and malignancy (27-29).

Mycophenolate is another transplant medication used for sarcoidosis (30;31). It has less toxicity than azathioprine (28;32). However, one still has to monitor for infections. It has been proposed as more effective than other anti-metabolites for neurosaroidosis (33;34). However, one study found patients were significantly more likely to have mycophenolate stopped over time compared to methotrexate (35).

In the past, cyclophosphamide (CYC) has been used for treating refractory neurosarcoidosis (36;37). Cyclophosphamide is an alkylating agent associated with a variety of toxicities including bone marrow suppression, increased susceptibility to infection, fertility issues, hemorrhagic cystitis, increased risk of malignancy especially bladder cancer, and rarely pulmonary toxicity (38-42). Therefore the clinician should consider less toxic alternative medications whenever possible.

Anti-tumor necrosis factor (anti-TNF) antibodies: Inflximab is the most widely studied and used monoclonal antibody used for treatment of sarcoidosis. In a double blind placebo controlled trials, it was

found to be superior to placebo in treating chronic pulmonary sarcoidosis (43;44) and chronic cutaneous sarcoidosis (45). In addition, there have been several large retrospective series reporting its effectiveness in chronic skin (46), neurologic (47;48), and pulmonary manifestations (49;50). Biosimilars seem to have the same response rate as infliximab (51). Guidelines have been established to help identify which patients to treat, dosing, and monitoring (19). A major limitation of infliximab is increased risk for infections, especially tuberculosis (52), and allergic reactions (53).

Adalimumab is associated with less toxicity. However, the reported experience in sarcoidosis is less robust. It was found more effective than placebo in treating chronic cutaneous sarcoidosis (54). For pulmonary disease, there have been some case series reporting the drug was effective in chronic disease (55;56). Many clinicians feel adalimumab is less potent than infliximab in treating sarcoidosis (57). The drug can be an effective alternative when a patient develops a systemic reaction to infliximab (58).

Golimumab is another anti-TNF monoclonal antibody. In a double blind placebo controlled trial, the drug was no better than placebo in treating the disease (59). While this may have been because of the relatively lower anti-TNF dose of the drug, this drug is not recommended for most patients with advanced sarcoidosis. Etanercept, a TNF receptor antagonist, has also been shown to have a lower rate of response than that seen with the anti-TNF antibodies (60;61).

Rituximab was originally developed as a treatment for non Hodgkins lymphoma. Over the past ten years, it has been used increasingly in nonmalignant conditions, including sarcoidosis. Small case series and reports suggest the drug has a role as a third line therapy for advanced pulmonary, eye, neurologic, or cardiac disease (62-65). Current recommendation is to place patients who respond to rituximab on a maintenance regimen (64). The drug is associated with a lower rate of drug withdrawal than anti-TNF agents (66).

Repository corticotropin injection (RCI) was initially approved for sarcoidosis and many other conditions in the early 1950s. Originally it was felt the only mechanism of action was stimulation of the adrenal cortex to release cortisol and the drug was felt to be equivalent of oral glucocorticoids (8;67). Recent studies of non sarcoidosis diseases have suggested that RCI may have other mechanisms of action through alternative melanocortin receptors (68;69). There have been recent reports of the effectiveness of RCI as a steroid sparing agent in advanced sarcoidosis (70;71).

Hydroxychloroquine and chloroquine are antimalarial agents that have been used to treat sarcoidosis for many years (72). These agents have been useful to treat skin manifestations (73;74) and abnormalities of calcium metabolism (75;76). Hydroxychloroquine is the preferred agent at this time because of reduced ocular toxicity. However, it still may lead to significant vision loss and routine screening is recommended with this drug (77).

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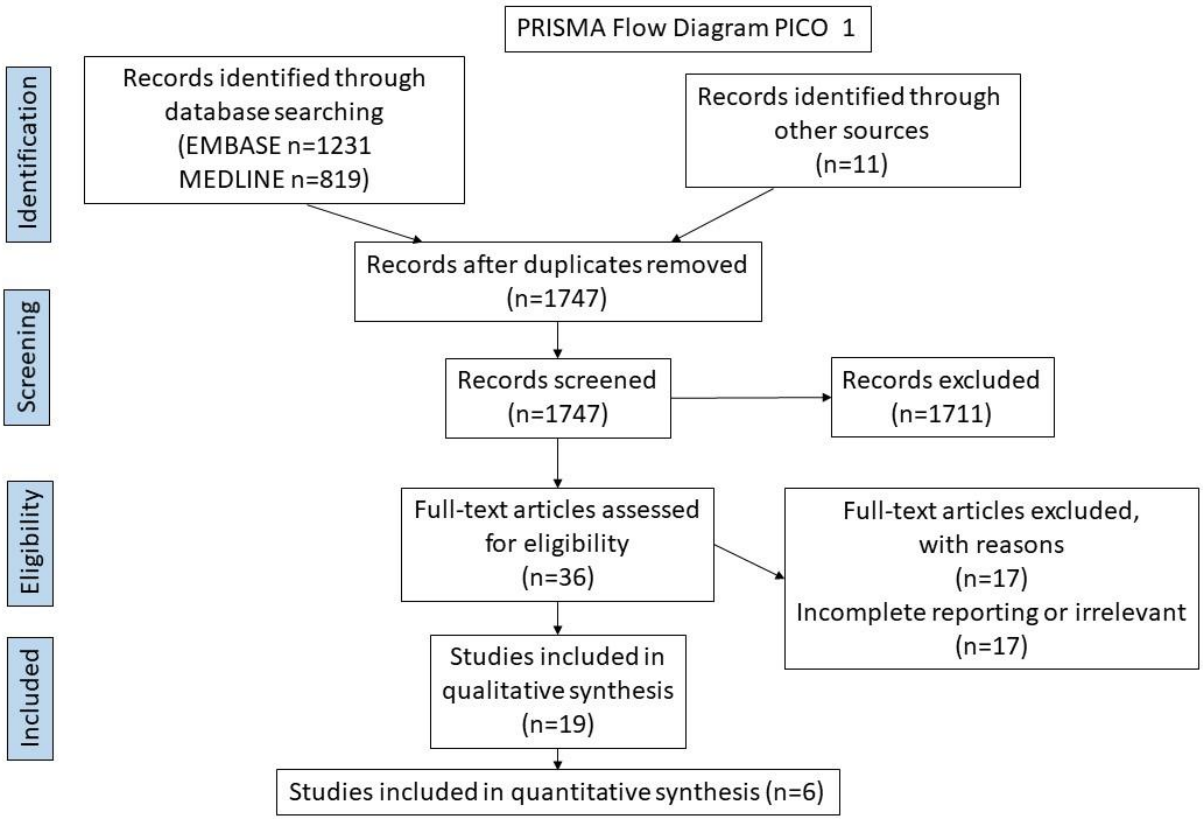
Supplement S-2

Evidence Summaries and Evidence to Decision Tables for all PICOs.

PICO 1



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097; For more information, visit www.prisma-statement.org.

Evidence Summaries for PICO 1

Question: Oral Glucocorticoids compared to Placebo for Sarcoidosis

Setting: Treatment naive patients with chronic symptomatic pulmonary sarcoidosis.

Bibliography: James 1967, Israel 1973, Pietinalho 1999, Pietinalho 2002, Selroos 1979, Zaki 1987 (1-6)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral Glucocorticoids	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical, radiological & biochemical improvement (clinical judgement) (follow up: up to 2 years)												
3	randomised trials	serious [a]	not serious	not serious	Not serious	none	38/68 (55.9%)	14/66 (21.2%)	**RR 2.44** (1.40 to 4.25)	**305 more per 1,000** (from 85 more to 689 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical, radiological & biochemical deterioration (overall clinical judgement) (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	3/27 (11.1%)	7/24 (29.2%)	**RR 0.38** (0.11 to 1.31)	**181 fewer per 1,000** (from 260 fewer to 90 more)	⨁⨁◯◯ LOW	CRITICAL
Radiological improvement (clinical judgement) (follow up: up to 2 years)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	102/164 (62.2%)	68/151 (45.0%)	**RR 1.35** (1.11 to 1.64)	**158 more per 1,000** (from 50 more to 288 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Spirometric improvement (FVC improvement) (follow up: up to 2 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral Glucocorticoids	Placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	35/113 (31.0%)	25/93 (26.9%)	**RR 1.09** (0.70 to 1.70)	**24 more per 1,000** (from 81 fewer to 188 more)	⨁⨁◯◯ LOW	CRITICAL

DLCO improvement (follow up: 2 years)

1	randomised trials	serious [a]	not serious	not serious	Serious c	none	23/53 (43.4%)	12/34 (35.3%)	**RR 1.23** (0.71 to 2.13)	**81 more per 1,000** (from 102 fewer to 399 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Outcomes not assessed

Patient well-being: Critical

Changes in PET/CT chest imaging: Important

6 minute walk distance: Important

Quality of life: Important

Adverse events: Critical

Explanations

a. Randomization and concealment methodology were inadequately reported.

b. Estimates are based on a limited study population

c. Estimated are based on a limited study population and testing not as reproducible as FVC.

ERS PICO 1 EtD tables

QUESTION

POPULATION:	Treatment naive patients with chronic symptomatic pulmonary sarcoidosis.
INTERVENTION:	Oral or inhaled glucocorticoids
COMPARISON:	Placebo or no treatment

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small • **Moderate** ○ Large ○ Varies ○ Don't know	**Oral glucocorticoids** **Overall response:** Overall response judged by a clinician based on clinical and radiological evaluation was available in 2 studies involving 134 patients (1;2). Oral glucocorticoids led to a larger proportion of patients experiencing clinical improvement RR 2.44 [1.40-4.25] in short term follow-up (3-6 months). There was also a trend towards less patients experiencing clinical deterioration (RR 0.38 [0.11-1.31]), in the short term. **CXR changes:** Based on 3 placebo controlled studies with an overall study population of 340 patients (1;3;6), use of oral glucocorticoids led to improvement in the radiographic changes, as judged by a clinician, in more patients than placebo. RR: 1.35 [1.11-1.64]. Moreover, significantly lower proportion of patients receiving oral glucocorticoids experienced a significant radiological deterioration RR: 0.39 [0.18-0.87]. **Lung function:** No statistically significant differences were observed in any of the identified studies (3;5;6)	The short-term nature of glucocorticoid efficacy data, However, these differences do not appear to persist in the long-term, 1-4 years after discontinuation of glucocorticoids, based on two studies with 80 patients (2;5).

Undesirable Effects

How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large • **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	No data on the undesirable effects of systemic or inhaled glucocorticoids were identified in the included randomized controlled trials (RCTs).	Although the adverse events of systemic and/or inhaled glucocorticoids have not been properly assessed in the research evidence answering this clinical question, toxicity is well known and include: A recent systematic review evaluated the safety of long-term systemic glucocorticoid exposure in 32 primary studies. It found that glucocorticoids users were 1.5-fold more likely to develop chronic adverse events such as sleep disturbance, migraine, cataract, hypertension and type 2 diabetes mellitus compared with nonusers (7). Even short-term use of systemic glucocorticoids (<30 days) is associated with an increased risk of sepsis (5-fold increase), venous thromboembolism (3-fold) and fracture (90% increase) (8).
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low **Low** Moderate ○ High ○ No included studies	Certainty of evidence is low- due to the increased risk of bias and imprecision (limited study population) of the available studies.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention • **Favors the intervention** ○ Varies ○ Don't know	**Oral glucocorticoids:** Available data suggest that oral glucocorticoids are associated with significant clinical and radiographic improvement of patients with sarcoidosis. In parallel, the administration of systemic glucocorticoids is associated with significant adverse events, which include severe infections, osteoporosis and fractures, type 2 diabetes, hypertension etc. **Inhaled glucocorticoids:** Currently available data do not support the use of inhaled glucocorticoids, as they do not appear to confer benefits to patients with sarcoidosis.	Systemic glucocorticoids are associated with moderate beneficial effects, that do not persist in the long-term after discontinuation, but also moderate adverse events.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or	**No specific studies were identified to**	Although we are not aware of any research evidence assessing how much people value the main outcomes, form the current

variability • **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**answer this question.**	clinical practice GDG considers that reduction in symptoms and delay in lung function decline would be considered important by patients. However, long-term use of systemic glucocorticoids is associated with moderate adverse events and adverse events and overall quality of life have been reported by patients as important (9).
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies X Don't know	**No specific studies were identified to answer this question.**	While systemic glucocorticoids are cheap and widely available drugs, there are significant costs related with adverse events caused by their long-term use (>1 month).
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies X Don't know	No specific studies were identified to answer this question.	Systemic glucocorticoids are globally available and cheap.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies • **Don't know**	No specific studies were identified to answer this question.	While the reduction in symptoms and delay in lung function progression would be considered important outcome, long-term use of systemic glucocorticoids is associated with significant adverse events. Patients with major involvement form pulmonary sarcoidosis, at higher risk of future mortality or permanent disability from sarcoidosis are anticipated to accept the intervention.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no		

○ Probably yes • **Yes** ○ Varies ○ Don't know		**Widely implemented already.**

SUMMARY OF JUDGEMENTS ORAL GLUCOCORTICOIDS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	X

CONCLUSIONS

Recommendation

For untreated patients with major involvement from pulmonary sarcoid, believed to be at higher risk of future mortality or permanent disability from sarcoidosis, we recommend the introduction of glucocorticoid therapy, to improve and/or preserve FVC and quality of life. (Strong recommendation, low quality of evidence).

Justification

Systemic glucocorticoid administration is associated with improved overall response, as judged by a clinician, based on clinical, radiological and biochemical evaluation. It is also associated with radiological improvement. In view of the well-known adverse events associated with systemic glucocorticoids, the decision to use glucocorticoids needs to be made based on severity of disease and patient symptoms (see next).

Subgroup considerations

In view of the well-known adverse-events associated with systemic glucocorticoids, we only recommend their use for people with major involvement from pulmonary sarcoidosis, believed to be at higher risk of future mortality or permanent disability from sarcoidosis.
Patients who do not meet these criteria, we recommend the institution of oral glucocorticoid therapy be considered on a case by case basis.

Implementation considerations

This intervention is already widely implemented.

Research priorities

There is an urgent need for accurate risk stratification in pulmonary sarcoidosis. Unmet needs include optimal pulmonary function thresholds, integrated with disease duration, and risk assessment for progression in higher risk disease. It is uncertain when higher risk disease is best managed with glucocorticoid monotherapy as opposed to combination therapy with second or third-line agents. The role of PET in rationalizing long-term therapy following initial stabilization of irreversible disease requires exploration in large cohorts.

A data-base is needed to quantify glucocorticoid therapy efficacy in patients with unacceptable loss of quality of life, explore the efficacy and adverse effects balance with the use of low dose glucocorticoid therapy, and evaluate the dose and duration driven by patient choice.

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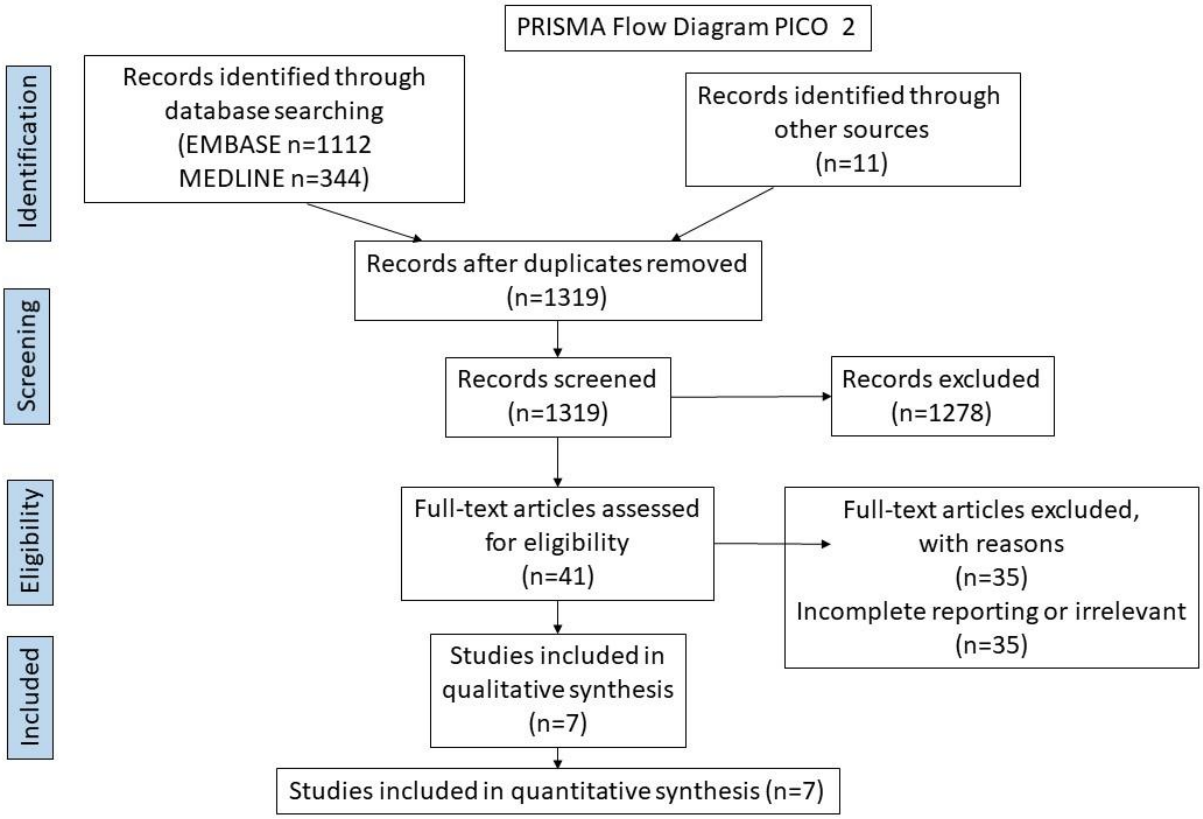
PICO 2



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097; For more information, visit www.prisma-statement.org.

Evidence Profile Tables for PICO 2

Question: Methotrexate for Pulmonary Sarcoidosis already treated with systemic glucocorticoids

Bibliography: Baughman 2000 (10)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Improvement in pulmonary function testing												
Adverse events during treatment (follow up: 12 months)												
1	randomised trials	Very serious [a]	not serious	not serious	serious [a]	none	8/16 (50.0%)	8/8 (100.0%)	**RR 0.53** (0.32 to 0.87)	**470 fewer per 1,000** (from 680 fewer to 130 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events during treatment: Respiratory infections (follow up: 12 months)												

1	randomised trials	very serious [a]	not serious	not serious	serious [a]	none	6/16 (37.5%)	4/8 (50.0 %)	**RR 0.75** (0.29 to 1.92)	**125 fewer per 1,000** (from 355 fewer to 460 more)	⨁◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The included study select patients with high risk of attrition bias and unclear risk of selection and allocation bias

b. This finding is based on a small number of patients.

Question: Infliximab 3mg/kg for Pulmonary Sarcoidosis already treated with systemic glucocorticoids and/or other immunosuppressives

Bibliography: Baughman 2006 (11)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Infliximab 3mg/kg**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of life (SGRQ change from baseline) at end of treatment (shows a trend towards smaller drop in SGRQ) (follow up: 24 weeks; assessed with: SGRQ)												
1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	46	45	-	MD **1.3 higher** (4.66 lower to 7.26 higher)	⨁◯◯ LOW	IMPORTANT
Breathlessness (Borg's Scale change from baseline) at end of treatment (shows a trend towards increased drop in Borg's Scale) (follow up: 24 weeks; assessed with: Borg's scale)												
1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	46	45	-	MD **0.1 lower** (4.67 lower to 4.47 higher)	⨁◯◯ LOW	IMPORTANT
6-MWT change from baseline (shows a trend towards longer 6-MWT distance) (follow up: 24 weeks)												

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	46	45	-	MD **23 metres higher** (4.91 lower to 50.91 higher)	⨁◯◯ LOW	IMPORTANT

Radiograph R-score (Shows a trend towards improved score) (follow up: 24 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	46	45	-	MD **1.33 lower** (7.2 lower to 4.54 higher)	⨁◯◯ LOW	IMPORTANT

All Adverse events during treatment (follow up: 24 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	39/45 (86.7%)	35/44 (79.5%)	**RR 1.09** (0.90 to 1.32)	**72 more per 1,000** (from 80 fewer to 255 more)	⨁◯◯ LOW	CRITICAL

Adverse events during treatment: Pneumonia (follow up: 24 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [b]	none	0/45 (0.0%)	0/44 (0.0%)	not estimable		⨁◯◯ LOW	CRITICAL

Serious adverse events during treatment (follow up: 24 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [b]	none	6/45 (13.3%)	5/44 (11.4%)	**RR 1.17** (0.39 to 3.57)	**19 more per 1,000** (from 69 fewer to 292 more)	⨁◯◯ LOW	CRITICAL

Mortality (follow up: 24 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [b]	none	0/45 (0.0%)	1/44 (2.3%)	not estimable		⨁◯◯ LOW	CRITICAL

FVC(%predicted) change from baseline (follow up: mean 24 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [b]	none	45	44	-	MD **2.7 % higher** (0.44 higher to 4.96 higher)	⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. This finding is based on a low number of patients.

Question: Infliximab for Pulmonary Sarcoidosis already treated with systemic glucocorticoids and/or other immunosuppressives

Bibliography: Baughman 2006 (11), Rossman 2006 (12)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Infliximab 5mg/kg**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Quality of life (SGRQ change from baseline) at end of treatment (shows a trend towards smaller drop in SGRQ) (follow up: 24 weeks; assessed with: SGRQ)												
1 (11)	randomised trials	Not serious	not serious	not serious	very serious [a]	none	47	45	-	MD **0.4 higher** (5.42 lower to 6.22 higher)	⨁◯◯ LOW	IMPORTANT
Quality of life (SF36 - Absolute value, Shows statistically but not clinically significant improvement) (follow up: 6 weeks; assessed with: SF-36)												
1 (11)	randomised trials	Not serious	not serious	not serious	very serious [a]	none	13	6	-	MD **0.71 higher** (0.01 higher to 1.41 higher)	⨁◯◯ LOW	IMPORTANT
Breathlessness (Borg's Scale change from baseline) at end of treatment (shows a trend towards increased drop in Borg's Scale) (follow up: 24 weeks; assessed with: Borg's Scale)												
1 (11)	randomised trials	Not serious	not serious	not serious	very serious [a]	none	47	45	-	MD **0.4 lower** (6.38 lower to 5.58 higher)	⨁◯◯ LOW	IMPORTANT

6-MWT change from baseline (shows a trend towards longer 6-MWT distance) (follow up: 24 weeks; assessed with: 6-MWT)

1 (11)	randomised trials	Not serious	not serious	not serious	very serious [a]	none	47	45	-	MD **7.3 higher** (22.22 lower to 36.82 higher)	⨁◯◯ LOW	IMPORTANT

Radiograph R-score (Shows a trend towards improved score) (assessed with: R-score)

1 (11)	randomised trials	Not serious	not serious	not serious	very serious [a]	none	47	45	-	MD **1.14 lower** (9.45 lower to 7.17 higher)	⨁◯◯ LOW	IMPORTANT

All Adverse events during treatment (follow up: range 6 weeks to 24 weeks)

2 (11;12)	randomised trials	Not serious	not serious	not serious	very serious [a]	none	39/59 (66.1%)	36/50 (72.0%)	**RR 0.99** (0.79 to 1.25)	**7 fewer per 1,000** (from 151 fewer to 180 more)	⨁◯◯ LOW	CRITICAL

Adverse events during treatment: Pneumonia (follow up: range 6 weeks to 24 weeks)

2 (11;12)	randomised trials	Not serious	not serious	not serious	very serious [a]	none	13/59 (22.0%)	0.1/50 (0.2%)	**RR 11.23** (1.71 to 73.74)	**20 more per 1,000** (from 1 more to 145 more)	⨁◯◯ LOW	CRITICAL

Serious adverse events during treatment (follow up: 24 weeks)

2 (11;12)	randomised trials	Not serious	not serious	not serious	very serious [a]	none	4/46 (8.7%)	5/44 (11.4%)	**RR 0.77** (0.22 to 2.67)	**26 fewer per 1,000** (from 89 fewer to 190 more)	⨁◯◯ LOW	CRITICAL

Mortality (follow up: 24 weeks)

1 (11)	randomised trials	Not serious	not serious	not serious	very serious [a]	none	0/46 (0.0%)	1/44 (2.3%)	**RR 0.32** (0.01 to 7.63)	**15 fewer per 1,000** (from 23 fewer to 151 more)	⨁◯◯ LOW	CRITICAL

FVC(%predicted) change from baseline (follow up: range 6 weeks to 24 weeks)

2 (11;12)	randomised trials	Not serious	not serious	not serious	very serious [a]	none	59	50	-	MD **2.9 % higher** (0.43 higher to 5.36 higher)	⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. This finding is based on a low number of patients.

Question: Golimumab for Pulmonary Sarcoidosis already treated with systemic glucocorticoids

Bibliography: Judson 2014 (13)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Golimumab**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		

FVC (change from baseline) at end of treatment (shows a trend towards smaller drop in FVC) (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	42	44	-	MD **1.3 lower** (5.87 lower to 3.27 higher)	⨁◯◯ LOW	CRITICAL

6-MWT change from baseline (shows a trend towards longer 6-MWT distance) (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	42	44	-	MD **1.99 meters lower** (42.39 lower to 38.41 higher)	⨁◯◯ LOW	IMPORTANT

Quality of life (SGRQ change from baseline) at end of treatment (shows a trend towards smaller drop in SGRQ) (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	42	44	-	MD **2.64 higher** (5.28 lower to 10.56 higher)	⨁◯◯ LOW	IMPORTANT

Percentage of patients with at least 50% reduction in OCS dose (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	31/38 (81.6%)	16/31 (51.6 %)	**RR 1.58** (1.09 to 2.29)	**299 more per 1,000** (from 46 more to 666 more)	⨁◯◯ LOW	CRITICAL

Percentage of patients who completely withdrew from OCS (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	11/38 (28.9%)	6/31 (19.4 %)	**RR 1.50** (0.62 to 3.59)	**97 more per 1,000** (from 74 fewer to 501 more)	⨁◯◯ LOW	CRITICAL

Serious adverse events (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	7/58 (12.1%)	9/55 (16.4 %)	**RR 1.36** (0.54 to 3.39)	**59 more per 1,000** (from 75 fewer to 391 more)	⨁◯◯ LOW	CRITICAL

Adverse events (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	53/58 (91.4%)	54/55 (98.2 %)	**RR 1.07** (0.99 to 1.17)	**69 more per 1,000** (from 10 fewer to 167 more)	⨁◯◯ LOW	CRITICAL

Adverse events: Infections (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	26/58 (44.8%)	29/55 (52.7 %)	**RR 1.18** (0.80 to 1.72)	**95 more per 1,000** (from 105 fewer to 380 more)	⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. This finding is based on a low number of patients.

Question: Ustekinumab for Pulmonary Sarcoidosis already treated with systemic glucocorticoids

Bibliography: Judson 2014 (13)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ustekinumab**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		

FVC (change from baseline) at end of treatment (shows a trend towards smaller drop in FVC) (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	46	44	-	MD **1.03 lower** (5.41 lower to 3.35 higher)	⨁◯◯ LOW	CRITICAL

6-MWT change from baseline (shows a trend towards longer 6-MWT distance) (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	46	44	-	MD **27.74 meters lower** (66.29 lower to 10.81 higher)	⨁◯◯ LOW	IMPORTANT

Quality of life (SGRQ change from baseline) at end of treatment (shows a trend towards smaller drop in SGRQ) (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	46	44	-	MD **5.25 higher** (2.31 lower to 12.81 higher)	⨁◯◯ LOW	IMPORTANT

Percentage of patients with at least 50% reduction in OCS dose (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	22/38 (57.9%)	16/31 (51.6 %)	**RR 1.12** (0.73 to 1.73)	**62 more per 1,000** (from 139 fewer to 377 more)	⨁◯◯ LOW	CRITICAL

Percentage of patients who completely withdrew from OCS (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	7/38 (18.4%)	6/31 (19.4 %)	**RR 0.95** (0.36 to 2.54)	**10 fewer per 1,000** (from 124 fewer to 298 more)	⨁◯◯ LOW	CRITICAL

Serious adverse events (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	10/60 (16.7%)	9/58 (15.5 %)	**RR 1.07** (0.47 to 2.45)	**11 more per 1,000** (from 82 fewer to 225 more)	⨁◯◯ LOW	CRITICAL

Adverse events (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	59/60 (98.3%)	54/58 (93.1%)	**RR 1.06** (0.98 to 1.14)	**56 more per 1,000** (from 19 fewer to 130 more)	⨁◯◯ LOW	CRITICAL

Adverse events: Infections (follow up: 28 weeks)

1	randomised trials	Not serious	not serious	not serious	very serious [a]	none	30/60 (50.0%)	29/58 (50.0%)	**RR 1.00** (0.70 to 1.43)	**0 fewer per 1,000** (from 150 fewer to 215 more)	⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. This finding is based on a low number of patients.

Question: Pentoxifylline for Pulmonary Sarcoidosis already treated with systemic glucocorticoids

Bibliography: Park 2009 (14)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pentoxifylline	Placebo	Relative (95% CI)	Absolute (95% CI)		

Number of patients experiencing at least one sarcoidosis flare (follow up: range 6 months to 10 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	Criteria poorly describe	5/12 (41.7%)	12/13 (92.3%)	**RR 0.45** (0.23 to 0.90)	**508 fewer per 1,000** (from 711 fewer to 92 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Number of patients experiencing at least one sarcoidosis flare, among those who were followed for at least 9 months (follow up: 10 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	Criteria poorly describe	3/9 (33.3%)	9/9 (100.0 %)	**RR 0.37** (0.16 to 0.87)	**630 fewer per 1,000** (from 840 fewer to 130 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Glucocorticoid sparing: Prednisolone free weeks (follow up: 10 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	13	14	-	MD **7 higher** (5.02 higher to 8.98 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Glucocorticoid sparing: Mean prednisolone dose throughout the study (follow up: 10 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	13	14	-	MD **4.64 lower** (6.08 lower to 2.84 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Mean prednisolone dose at last day of the trial (for those who completed 10 months) (follow up: 10 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	4	6	-	MD **8.9 lower** (9.75 lower to 8.05 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Improvement in 2 of the following pulmonary function tests: 15% improvement in FEV1 or 15% improvement in FVC or 20% improvement in DLCO, at any timepoint (follow up: 10 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/13 (0.0%)	0/14 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT

Improvement in 1 pulmonary function test (see previous outcome) and in dyspnoea severity, at any timepoint (follow up: 10 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/13 (7.7%)	0/14 (0.0%)	**RR 3.21** (0.14 to 72.55)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Adverse events in treatment duration (follow up: 10 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	12/13 (92.3%)	4/14 (28.6%)	**RR 3.23** (1.39 to 7.51)	**637 more per 1,000** (from 111 more to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The included study is of unclear risk of selection bias

b. This finding is based on a small number of patients and the line of effect is within the confidence interval.

Question: Cyclosporin for Pulmonary Sarcoidosis already treated with systemic glucocorticoids

Bibliography: Wyser 1997 (15)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciclosporin	Placebo	Relative (95% CI)	Absolute (95% CI)		

Improvement in 2 of the following pulmonary function tests: 15% improvement in FEV1 or 15% improvement in FVC or 20% improvement in DLCO or 1 pulmonary function test and dyspnoea severity (follow up: 3 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	11/19 (57.9%)	12/18 (66.7%)	**RR 0.87** (0.52 to 1.44)	**87 fewer per 1,000** (from 320 fewer to 293 more)	⨁◯◯◯ VERY LOW	CRITICAL

Improvement in 2 of the following pulmonary function tests: 15% improvement in FEV1 or 15% improvement in FVC or 20% improvement in DLCO or 1 pulmonary function test and dyspnoea severity (follow up: 9 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	10/19 (52.6%)	12/18 (66.7%)	**RR 0.79** (0.46 to 1.35)	**140 fewer per 1,000** (from 360 fewer to 233 more)	⨁◯◯◯ VERY LOW	CRITICAL

Improvement in 2 of the following pulmonary function tests: 15% improvement in FEV1 or 15% improvement in FVC or 20% improvement in DLCO or 1 pulmonary function test and dyspnoea severity (follow up: 18 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	7/12 (58.3%)	8/12 (66.7%)	**RR 0.88** (0.47 to 1.63)	**80 fewer per 1,000** (from 353 fewer to 420 more)	⨁◯◯◯ VERY LOW	CRITICAL

Adverse events: Infections (follow up: 18 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	11/19 (57.9%)	6/18 (33.3%)	**RR 1.74** (0.81 to 3.70)	**247 more per 1,000** (from 63 fewer to 900 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The included study is of high risk of performance bias and unclear risk of selection and allocation bias

b. This finding is based on a very limited overall study population. And large confidence intervals.

Outcomes not studied

Important:

Patient well-being

Changes in PET/CT chest imaging

PICO 2 EtD table

QUESTION ***In patients with pulmonary sarcoidosis should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?***

POPULATION:	Patients with chronic symptomatic pulmonary sarcoidosis who have been treated with glucocorticoids and have continued active disease
INTERVENTION:	Infliximab (3 or 5 mg/kg); Golimumab; Ustekinumab; Pentoxifylline; Cyclosporin; Methotrexate
COMPARISON:	Remain on glucocorticoid therapy

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small X Moderate ○ Large ○ Varies ○ Don't know	**Methotrexate**: No evidence of improved clinical outcomes. However, there was a significant decrease in the risk of adverse events compared to prednisone. **Infliximab** 5mg/kg: Significantly improved FVC(%predicted): MD 2.90% [0.43, 5.36]. Statistically but not clinically significant improvement in quality of life (SF36): MD 0.71 [0.01-1.41]. 3mg/kg: Significantly improve FVC(%predicted): MD 2.90% [0.43 – 5.30]. A trend towards increased 6-MWT distance: MD 23 [-4.92 - 50.91]. **Golimumab**: Patients on active drug more likely to have 50% or greater reduction in oral glucocorticoid dose: RR 1.58 **Ustekinumab**: No evidence of improved outcomes. **Pentoxifylline**: Lower number of patients experiencing at least one sarcoidosis flare: RR 0.43	**Methotrexate vs. placebo** Methotrexate was associated with a requirement of lower maintenance dose of systemic glucocorticoids and a decreased weight gain compared to control.

	[0.23-0.90]. (RR 0.37 [0.16-0.87], among those who were followed for at least 9 months). (not a CRITICAL outcome) Better glucocorticoid sparing effects - more weeks off-glucocorticoids: MD 7 [5.02-8.98] and lower mean prednisone dose throughout the study: MD 4.64 [2.84-6.08] (for those who completed 10 months of follow-up: MR 8.9 [8.05-9.75]). (not a CRITICAL outcome) **Cyclosporin**: No evidence of improved outcomes	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Methotrexate ○ Large ○ Moderate ○ Small X Trivial ○ Varies ○ Don't know **Infliximab** ○ Large ○ Moderate X Small ○ Trivial ○ Varies ○ Don't know **Golimumab** ○ Large ○ Moderate ○ Small X Trivial ○ Varies ○ Don't know **Ustekinumab** ○ Large ○ Moderate X Small ○ Trivial ○ Varies ○ Don't know **Pentoxifylline** ○ Large X Moderate	**Methotrexate**: No evidence of increased AE **Infliximab** Combined 3 and 5mg/kg : More adverse events: RR 11.23 [1.71-73.74]. No difference in SAE and mortality (11). **Golimumab**: No differences in AE, SAE or infections **Ustekinumab**: A trend towards increased risk of infections: RR 1.06 [0.98-1.14]. No other evidence of increased AE **Pentoxifylline**: Higher risk of adverse events: RR 3.23 [1.39-7.51]. **Cyclosporin**: A trend towards increased risk of infections: RR 1.74 [0.81-3.7].	Although the adverse events from these drugs have not been properly assessed in the research evidence answering this clinical question, toxicity is well known in treating other conditions.

○ Small ○ Trivial ○ Varies ○ Don't know **Cyclosporin** ○ Large ○ Moderate Small ○ Trivial ○ Varies X Don't know	-	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Methotrexate **X** Very low Low ○ Moderate ○ High ○ No included studies **Infliximab:** Very low X **Low** ○ Moderate ○ High ○ No included studies **Goolibmumab:** • **Very low** ○ Low ○ Moderate ○ High ○ No included studies **Ustekinumab:** • **Very low** ○ Low ○ Moderate ○ High ○ No included studies **Pentoxifylline:** • **Very low** ○ Low ○ Moderate ○ High ○ No included studies **Cyclosporin:** • **Very low** ○ Low ○ Moderate ○ High ○ No included studies	**See evidence profiles and section summary**	The quality of evidence was VERY LOW due to risk of bias and imprecision across all critical outcomes from all comparisons.
Balance of effects		

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Methotrexate ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison X Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know **Infliximab** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison X Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know **Golibmumab** ○ Favors the comparison ○ Probably favors the comparison X Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know **Ustekinumab** ○ Favors the comparison ○ Probably favors the comparison x Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the	**See evidence profiles and section summary** –	

intervention ○ Varies ○ Don't know **Pentoxifylline** ○ Favors the comparison ○ Probably favors the comparison x Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know **Cyclosporin** ○ Favors the comparison ○ Probably favors the comparison x Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	_	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability **•No important uncertainty or variability** ○ No known undesirable outcomes	We found not studies specifically evaluation these drugs in this area.	Although there is no research evidence assessing how much people value the main outcomes, the current clinical practice considers that many patients value exercise capacity, symptoms and quality of life over other objective test such as pulmonary function tests or radiological assessment. A survey among sarcoidosis patients identified the quality of life and function were most important factors, with adverse events less important (9)

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Methotrexate ○ Large costs x Moderate costs ○ Negligible costs and savings	We found no specific studies regarding costs of these drugs in sarcoidosis.	Judgement based on cost for other conditions. Methotrexate and cyclopsporin are of moderate cost, including cost f monitoring blood work. Infliximab, golibmumab, and uskinumab are very expensive. Pentoxifylline is relatively inexpensive.

○ Moderate savings ○ Large savings ○ Varies ○ Don't know **Infliximab** X Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know **Golibmumab** X Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know **Ustekinumab** X Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know **Pentoxifyllline** ○ Large costs X Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know **Cyclosporin** Large costs X Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

Methotrexate ○ Reduced ○ Probably reduced ○ Probably no impact X Probably increased ○ Varies ○ Don't know **Infliximab** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased x Increased ○ Varies ○ Don't know **Golimumab** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased x Increased ○ Varies ○ Don't know **Ustekinumab** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased x Increased ○ Varies ○ Don't know **Pentoxifyllline** ○ Reduced ○ Probably reduced ○ Probably no impact X Probably increased Increased ○ Varies ○ Don't know **Cyclosporin** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased x Increased ○ Varies ○ Don't know	**We found not studies specifically evaluation these drugs in this area.**	The GDG considers that the recommendations would probably have no impact on equity. Methotrexate: Methotrexate is globally available and cheap Infliximab (3 and 5 mg/kg): In places with no universal health coverage and no generic equivalent it may generate inequities Golimumab: No generic equivalent, in places wiht no universal health coverage it may generate inequities Ustekinumab: No generic equivalent, in places with no universal health coverage it may generate inequities Pentoxifylline: Pentoxifylline is globally available and cheap Cyclosporin: Cyclosporin is globally available and cheap

Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	**Research evidence**	**Additional considerations**
Methotrexate ○ No	We found not studies specifically evaluation these drugs in	The GDG considers that the recommendation is acceptable to key stakeholders.

○ Probably no x Probably yes ○ Yes ○ Varies ○ Don't know **Infliximab** ○ No ○ Probably no x Probably yes ○ Yes ○ Varies ○ Don't know **Golimumab** ○ No X Probably no Probably yes ○ Yes ○ Varies ○ Don't know **Ustekinumab** ○ No X Probably no Probably yes ○ Yes ○ Varies ○ Don't know **Pentoxifylline** ○ No XProbably no Probably yes ○ Yes ○ Varies ○ Don't know **Cyclosporin** ○ No x Probably no Probably yes ○ Yes ○ Varies ○ Don't know	sarcoidosis.	Methotrexate: Likely to be acceptable to key stakeholders. Infliximab (3 and 5 mg/kg): IV administration would be less acceptable for some patients. Off-label indication may not be acceptable for clinicians or policymakers Golimumab: IV administration would be less acceptable for some patients. Off-label indication may not be acceptable for clinicians or policymakers Ustekinumab: IV administration would be less acceptable for some patients Off-label indication may not be acceptable for clinicians or policymakers Pentoxifylline: Pentoxifylline would place patients at risk of significant side effects, for not significant benefit. Cyclosporin: Cyclosporin would place patients at risk of significant side effects, for not significant benefit.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Methotrexate ○ No ○ Probably no x Probably yes ○ Yes ○ Varies ○ Don't know	**We found not studies specifically evaluation these drugs in sarcoidosis.**	Methotrexate: Widely implemented already Infliximab (3 and 5 mg/kg): Widely implemented already Golimumab: Not available in some countries Ustekinumab: Not available in some countries

Infliximab ○ No ○ Probably no x Probably yes ○ Yes ○ Varies ○ Don't know **Golimumab** ○ No X Probably no Probably yes ○ Yes ○ Varies ○ Don't know **Ustekinumab** ○ No X Probably no Probably yes ○ Yes ○ Varies ○ Don't know **Pentoxifylline** ○ No XProbably no Probably yes ○ Yes ○ Varies ○ Don't know **Cyclosporin** ○ No x Probably no Probably yes ○ Yes ○ Varies ○ Don't know		Pentoxifylline: Implemented for other diseases. Cyclosporin: Implemented for other diseases

SUMMARY OF JUDGEMENTS METHOTREXATE

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

SUMMARY OF JUDGEMENTS INFLIXIMAB

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

SUMMARY OF JUDGEMENTS GOLIMUMAB

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

SUMMARY OF JUDGEMENTS USTEKINUMAB

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

SUMMARY OF JUDGEMENTS PENTOXIFYLLINE

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

SUMMARY OF JUDGEMENTS CYCLOSPORIN

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	•	○

CONCLUSIONS

Recommendation

For patients with 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, we suggest the addition of methotrexate to improve and/or preserve FVC and QoL. (Conditional recommendation, very low quality of evidence).

For patients with 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, we suggest the addition of infliximab to improve and/or preserve FVC and QoL. (Conditional recommendation, low quality of evidence).

No recommendation could be made for cyclosporine, pentoxifylline, golimumab, or ustekinumab as randomized trials showed no benefit over placebo (13-16). These drugs should be considered on a case by case basis.

Justification

Methotrexate can reduce the required maintenance dose of systemic glucocorticoids, thus preventing the adverse events associated with their prolonged use. Infliximab use is associated with a significant improvement in the FVC and statistically but not clinically significant improvement in quality of life, without posing an increased risk for serious adverse events.

Golimumab and pentoxifylline have been associated with modest clinical benefits. Ustekinumab and ciclosporin were not shown to be beneficial. In view of the demonstrated adverse events of these treatments, the panel did not feel that they should be used routinely, but only on a case-by-case basis.

Subgroup considerations

In view of the well-known adverse events associate with all immunosuppressives, we only recommend the use of methotrexate or infliximab for people with major involvement from pulmonary sarcoidosis who have been treated with glucocorticoids and have continued active disease or unacceptable side effects from glucocorticoids.

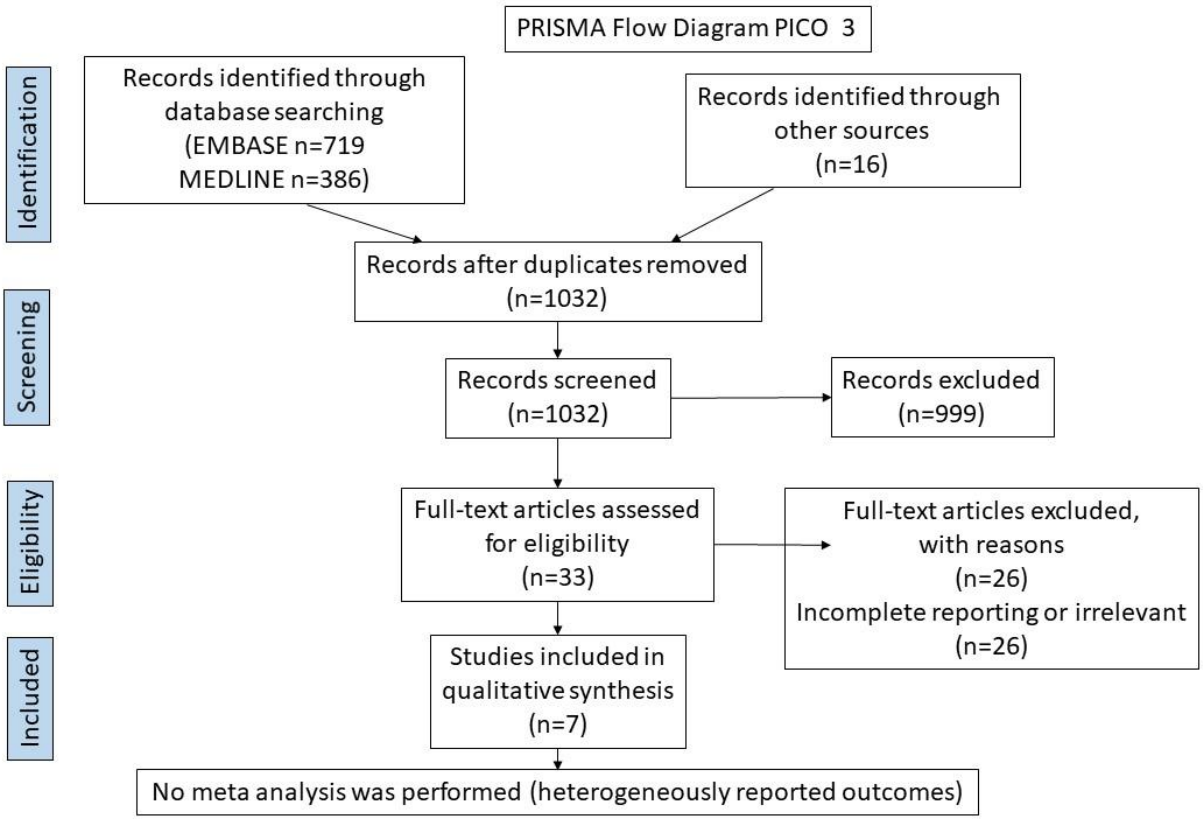
Implementation considerations

These interventions are already widely implemented

Research priorities

Additional studies are needed to evaluate the efficacy, safety and cost efficiency of rituximab, repository corticotropin injection, anti-TNF biosimilars and other agents. Newer endpoints, including change in PET and quality of life, need to be validated.

PICO 3



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097; For more information, visit www.prisma-statement.org.

Evidence table

Question:

In patients with cutaneous sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?

Setting: Outpatient

Bibliography: Ahmad (17), Chang (18), Chong (19), Collin (20), Tong (21), Ungprasert (22), Stagaki (23)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Clinical remission (assessed with: Investigator assessment)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
6	observational studies	serious (17-22;24) [a]	not serious	serious [b]	very serious [ab]	none	Ahmed (2006) (17): 21 patients; 20 with systemic evaluation. 16 had pulmonary sarcoid. 14/21 with adequate f/u. Complete remission in 3/14 with NSAID alone; 5/14 with GC alone; 4/14 with a recurrent disease with GC; 2/14 with partial remission with NSAID. I Chang (2012) (18): 5/10 pts with cutaneous sarcoidosis: 4/5 with complete response to GC. 1/5 partial response. I Chong (2005) (19): 25 patients: 5/25 complete remission, 20/25 partial remission. Various treatments used (topical in 20), systemic GC in 9/25. I Collin (2010) (20): 34 pts.; treatment described for 21: 9 received GC for extracutaneous. 5 for cutaneous (4/5 GC -->	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Remission of lupus pernio (follow up: range 18 days to 1659 days; assessed with: Clinical response)									
1	observational studies	serious[a]	not serious	serious [a]	not serious	none	116 treatment courses in 54 pts. with lupus pernio (different treatments): GC alone in 35 courses: 20% complete resolution, 80% improvement, no change or worse. (23)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Outcomes not assessed

Physician global assessment: Important

Quality of life: Critical

Adverse events: Critical

Explanations

a. Non-randomized study

b. no direct comparison of GC vs. no immunosuppression

c. No numerical values for treatment responses given

QUESTION

In patients with cutaneous sarcoidosis, should glucocorticoid treatment be used versus no glucocorticoid therapy?	
POPULATION:	extra-pulmonary sarcoidosis (skin)
INTERVENTION:	glucocorticoids
COMPARISON:	no glucocorticoid
MAIN OUTCOMES:	Clinical remission ; Remission of lupus pernio ;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes X Yes Varies ○ Don't know		Overall, there is low or very low quality evidence that GC treatment is efficacious in cutaneous sarcoidosis. This is limited by the absence of randomized trials in this area

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Ahmed (2006) (17): 21 patients; 20 with systemic evaluation. 16 had pulmonary sarcoid. 14/21 with adequate f/u. Complete remission in 3/14 with NSAID alone; 5/14 with GC alone; 4/14 with a recurrent disease with GC; 2/14 with partial remission with NSAID. Chang (2012) (18): 5/10 pts with cutaneous sarcoidosis: 4/5 with complete response to GC. 1/5 partial response. Chong (2005) (19): 25 patients: 5/25 complete remission, 20/25 partial remission. Various treatments used (topical in 20), systemic GC in 9/25. Collin (2010) (20): 34 pts.; treatment described for 21: 9 received GC for	

	extracutaneous. 5 for cutaneous (4/5 GC --> 2/4 complete remission, 2/4 complete remission with GC + HCQ) Tong (2013) (21): 36 pts.; follow-up data in 31 pts.; improvement in 15/31 with GC + other agents. No data on GC alone available. Ungprasert (2016) (22): 62/345 incident cases with skin sarcoidosis: GC in 36% --> resolution after 2 years Response to treatments was favorable with a complete response by 2 years after diagnosis in 84% of systemic sarcoidosis with sarcoidosis-specific cutaneous lesions, 96% of systemic sarcoidosis with EN and 96% of isolated cutaneous sarcoidosis.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Not reported in the identified studies	While not specifically reported in the included studies, the long-term adverse effects of GC are well-known and pose patients at significant risk for long-term complications.

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
XVery low Low ○ Moderate ○ High ○ No included studies		There are only retrospective observational trials available. In these studies, GCs were efficacious for the improvement of skin sarcoidosis in the majority of cases. No randomized controlled trials including a placebo group were identified.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No studies	While cutaneous sarcoidosis can be disfiguring and cosmetically important, it is rarely or never life-threatening compared to other sarcoidosis manifestations. This question, however, has not been addressed in the analyzed studies but has certainly to be taken into account when treating patients with a predominant skin manifestation. In a large survey of patients with sarcoidosis, improvement in quality of life is more important than adverse reaction (9).

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison Probably favors the comparison ○ Does not favor either the intervention or the comparison X Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		For patients with cosmetically important cutaneous sarcoidosis, the use of systemic GC are effective. Long term use may lead to significant toxicity.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies x Don't know	No specific studies were identified to answer this question.	GC are inexpensive. Cost is not an issue in this specific question.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low Low ○ Moderate ○ High x No included studies	No specific studies were identified to answer this question.	Topical/oral glucocorticoids are not expensive.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies X No included studies	No specific studies were identified to answer this question.	Although there is no research evidence supporting this with data, GC treatment is relatively inexpensive and widely available compared to other treatments. Since toxicity with prolonged therapy is significant, costs caused by the long-term side effects should be taken into consideration.

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reducedProbably no impact ○ Probably increased ○ Increased ○ Varies X Don't know	No specific studies were identified to answer this question	No research available for this specific question. However, GC use is very accessible and inexpensive. Therefore, it is not expected to result in any significant health inequities in the sarcoidosis population.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no Probably yes ○ Yes X Varies ○ Don't know	No specific studies were identified to answer this question	Insurance companies usually reimburse GC treatment. However, there are important side effects that are often not well tolerated by patients. Physicians, on the other hand, are comfortable with GC treatments due to many years of experience with risks and benefits.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question	GC treatment is currently widely accepted as a standard of care treatment for skin sarcoidosis.

SUMMARY OF JUDGEMENTS ORAL GLUCOCORTICOIDS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	**x●**	○

CONCLUSIONS

Recommendation

For patients with chronic cutaneous sarcoidosis and cosmetically important active skin lesions which cannot be controlled by local therapy, we suggest oral glucocorticoids to reduce skin lesions. (Conditional recommendation, very low quality of evidence).

Justification

Overall justification

Skin lesions have been reported to reduce in number and extension or disappear when topical and/or oral GC was added, although desired effects are generally limited to the duration of treatment and recurrences are common. The side effects of GC therapy is related to dose and duration of treatment. There are no data from randomized controlled studies to support these observations.

Detailed justification
Resources required
GC treatment is inexpensive and widely available.

Feasibility
Implementation of GC treatment for skin sarcoidosis has been widely accepted.

Subgroup considerations

Topical GCs are generally considered to be beneficial for skin lesions of limited extension.

Systemic GCs remain the treatment of choice for extensive cosmetically important lesions.

Patients with lupus pernio receiving systemic GC achieve a complete resolution in a minority of cases and should be closely monitored.

Implementation considerations

The principal barrier to implementation of treatment with topical or oral GC for skin sarcoidosis is represented by the ethical concerns related to the comparator (true placebo or other drugs with less evidence). Skin lesions, especially those which are cosmetically relevant, can lead to permanent scars and it would be unethical to design studies with a true placebo group as a control.

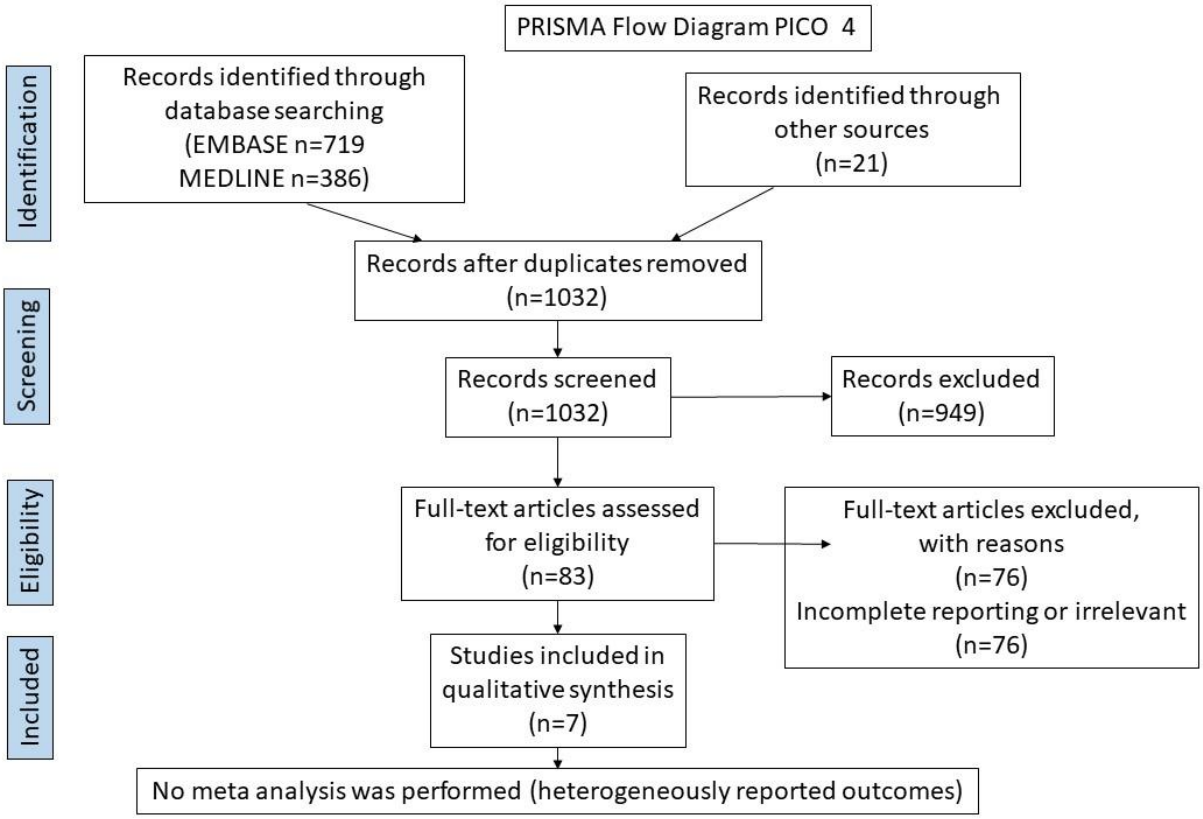
Monitoring and evaluation

Local and systemic side effects should be systematically evaluated in patients with long-term GC treatment.

Research priorities

Further research is needed to confirm the existing evidence on the effects of topic and oral GC in skin sarcoidosis. Cutaneous sarcoidosis activity and morphology assessment tools combined with ultrasound examinations should be used systematically in order to quantify the quality and magnitude of changes of the skin lesions and quality of life under treatment.

PICO 4



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097; For more information, visit www.prisma-statement.org.

PICO4: ***In patients with cutaneous sarcoidosis, should one add other immunosuppressive treatment when treatment with glucocorticoids have not been effective?***

4 a. Infliximab

Date:071518
Question: Patients with extra-pulmonary sarcoidosis failing standard therapy treated with immunosuppressives versus placebo
Setting: Outpatient
Bibliography: Baughman 2016, Baughman 2006, Droitcourt 2014, Judson 2014, Judson 2008, Pariser 2013 (11;13;25-28)

Certainity of Assessment							Number of Lesions		Effect	Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab for 24 weeks	Placebo for 24 weeks	Median		
Skin lesion assessment: SASI Erythema (25)											

1	randomised trials	Serious [1]	not serious	not serious	Serious [3]	N for skin lesions not patients	19	14	0 (1to -2) versus -1 (0 to -2)	⊕⊕◯◯ LOW	IMPORTANT
Skin lesion assessment: SASI Induration (25)											
1	randomised trials	Serious [1]	not serious	not serious	Serious [3]	N for skin lesions not patients	21	14	-1 (1to -3) versus 0 (0 to -2)	⊕⊕◯◯ LOW	IMPORTANT
Skin lesion assessment: SASI Desquamation (25)											
1	randomised trials	Serious [1]	not serious	not serious	Serious [3]	N for skin lesions not patients	12	10	-1 (1to -2) versus 0 (0 to -2)	⊕⊕◯◯ LOW	IMPORTANT
Skin lesin assessment: SASI Area Involved (25)											
1	randomised trials	Serious [1]	Not serious	not serious	Serious [3]	N for skin lesions not patients	26	15	-1 (0 to -4) versus 0 (0 to -2)	⊕⊕◯◯ LOW	IMPORTANT

Certainity of Assessment

							Number		**Effect**	**Quality**	**Importance**
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab for 24 weeks	Placebo for 24 weeks	Mean (+/- SD)		
Quality of life assessment: SF 36 PCS (25)											
1	randomised trials	Serious [1]	not serious	not serious	Serious [3]	N for patients, skin disease	12	5	3.6 (+/- 8.87) versus -2.1 (+/- 6.83)	⊕⊕◯◯ LOW	CRITICAL
Quality of life assessment: SF 36 MCS (25)											
1	randomised trials	Serious [1]	not serious	not serious	Serious [3]	N for patients, skin disease	12	5	-0.6 (+/- 7.42) versus -3.8 (+/- 5.62)	⊕⊕◯◯ LOW	CRITICAL

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thalidomide for 3 months	Placebo for 3 months	Mean (+/- SD)		
Skinlesion assessment: Skindex score (26)											

1	randomised trials	Not serious	not serious	not serious	Serious[3]	Patients with skin disease	20	19	65.2 (+/- 21.5) versus 67.4 (+/- 27.5)	⊕⊕⊕◯ MODERATE	IMPORTANT

Quality of Assessment	Number of Lesions	Effect	Quality	Importance

Certainity of Assessment

Quality assessment							**Number**		**Effect**	**Quality**	**Importance**
							№ of patients				
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ustekinumab for 28 weeks	Placebo for 28 weeks	Mean (+/- SD)		
Skin lesion assessment: Target lesion score (13)											
1	randomised trials	Not serious [2]	not serious	not serious	Serious[3]	N for patients, skin disease	21	20	-1.2 (NR) versus -1.4 (NR)	⊕⊕⊕◯ MODERATE	IMPORTANT
Skin lesion assessment: SASI (13)											
1	randomised trials	Not serious [2]	not serious	not serious	Serious [3]	N for patients, skin disease	21	20	-0.5 (NR) versus -0.52 (NR)	⊕⊕⊕◯ MODERATE	IMPORTANT

Certainity of Assessment

							Number		**Effect**	**Quality**	**Importance**
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Golimumab for 28 weeks	Placebo for 28 weeks	Mean (+/- SD)		
Skin lesion assessment: Target lesion score (13)											
1	randomised trials	Not serious [2]	not serious	not serious	Serious [3]	N for patients, skin disease	17	20	-2.3 (NR) versus -1.4 (NR)	⊕⊕⊕◯ MODERATE	IMPORTANT
Skin lesion assessment: SASI (13)											
1	randomised trials	Not serious [2]	not serious	not serious	Serious [3]	N for patients, skin disease	17	20	-2.57 (NR) versus -0.52 (NR)	⊕⊕⊕◯ MODERATE	IMPORTANT
№ of	Study design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Infliximab for	Placebo for	Mean (range)		

studies		bias				considerations	24 weeks	24 weeks			
Skin lesion assessment: ePost score (13)											
1	randomised trials	Serious [1]	not serious	not serious	not serious	Patients with chronic sarcoidosis	93	45	2.09(0.32) versus 3.7 -0.85	⊕⊕⊕◯ MODERATE	IMPORTANT

1. Unclear randomization methods and allocation concealment. Some authors employees of industry sponsor.
2. Unclear randomization methods and allocation concealment.
3. Small number of patients.

4b CLEAR

Date:090619

Question: Patients with Chronic cutaneous sarcoidosis treated with antimycobacterial agents versus placebo

Setting: Outpatiet

Bibliography: Drake 2013 (29)

Certainity of Assessment

							Number		**Effect**	**Quality**	**Importance**
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CLEAR for 8 weeks	Placebo for 8 weeks	Mean (+/- SD)		
Skin lesion assessment: Index lesion diameter (29)											
1	randomised trials	not serious	not serious	not	Serious[3]	Patients with chronic cutaneous sarcoidosis	14	15	-8.4 (14.0) versus 0.07 -3.2	⊕⊕⊕◯ MODERATE	IMPORTANT
Skin lesion assessment: SASI severity (29)											
1	randomised trials	Not serious	not serious	not	Serious[3]	Patients with chronic cutaneous sarcoidosis	14	15	-2.9 (2.5) versus -0.6 -2.1	⊕⊕⊕◯ MODERATE	IMPORTANT

1. Unclear randomization methods and allocation concealment. Some authors employees of industry sponsor.
2. Unclear randomization methods and allocation concealment.

3.Small number of patients.

QUESTION

POPULATION:	Patients with cutaneous sarcoidosis unresponsive to glucocorticoids
INTERVENTION:	Addition of immunosupressive treatment
COMPARISON:	Remain on glucocorticoids

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know **Thalidomide** X Trivial ○ Small Moderate ○ Large ○ Varies ○ Don't know **Ustekinumab** X Trivial ○ Small Moderate ○ Large ○ Varies ○ Don't know **Golimumab** XTrivial ○ Small Moderate ○ Large ○ Varies	**See evidence profiles** **Infliximab:** One study demonstrates significant improvement in SASI desquamation, one study improved ePOST (25;27). **Thalidomide:** no improved outcomes (30) **Ustekinumab:** no improved outcomes (13) **Golimumab:** no improved outcomes (13) **CLEAR:** One study demonstrated improvement in SASI (29)	Moderate effect for infliximab and CLEAR Trivial for other drugs

○ Don't know **CLEAR** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**See evidence profiles** **Infliximab:** One of 2 studies reported infusion site reactions in both 2.3% of placebo and active drug infusions (25;27). **Thalidomide:** Neuropathy in 1 of 15 (0.7%) patients (30). **Ustekinumab: For the entire study group of 60 ustekinumab treated patients,** pneumonia (5%), injection site reactions (5%), acute respiratory failure (1.7%) (13). **Golimumab: For the entire study group of 55 golimumab treated patients,** pneumonia (1.8%), injection site reactions (20%), sepsis (1.8%) (13). **CLEAR:** Three of fourteen (21%) discontinued therapy for diarrhea, joint pain, insomnia. One patient discontinued drug for incorrect diagnosis	Patients treated with immunosuppressive agents are at risk for well documented complications. The studies examined were too small to realize all potential complications. Patients treated with CLEAR received four antibiotics with well known toxicity and interactions.

_		
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
All drugs ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**See evidence profiles**	Based on recent large randomized trial for pulmonary disease (16), task force did not recommend CLEAR regimen except on a case by case basis.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Infliximab ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the	**Infliximab** ● Probably favors the intervention with infliximab only. **Thalidomide, Uskinumab, golimumab, CLEAR:**	

comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know **Thalidomide, Uskinumab, golimumab, CLEAR:** ○ Favors the comparison ○ Probably favors the comparison X Does not favor either the intervention or the comparison Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Does not favor either the intervention or the comparison	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
All drugs ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	We did not specifically look for studies evaluating drugs in this area.	A survey among sarcoidosis patients identified the quality of life and function were most important factors, with adverse events less important (9)
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Infliximab, Thalidomide, Uskinumab, golimumab: ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know **CLEAR** Large costs X Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We did not specifically look for studies evaluating drugs in this area.	**Infliximab** Infliximab is an expensive treatment but has been shown to be cost effective in other conditions (31). The cost effectiveness in sarcoidosis has not been studied. **Thalidomide, Uskinumab, golimumab:** All these agents are expensive treatments **CLEAR:** These four antibiotics are of moderate cost

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
All drugs ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	We did not specifically look for studies evaluating drugs in this area	In the United States, the immunomodulatory agent infliximab is a high cost treatment. To the extent that at-risk populations have limited medical insurance coverage, equity might be expected to be effected.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
All drugs ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	We did not specifically look for studies evaluating drugs in this area	Patients are often willing to take for cosmetically important refractory disease Thalidomide is a teratogen and requires specific monitoring in most countries.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Infliximab ○ No ○ Probably no X Probably yes ○ Yes ○ Varies Don't know **Thalidomide, Uskinumab, golimumab:** ○ No ○ Probably no Probably yes ○ Yes ○ Varies X Don't know CLEAR ○ No ○ Probably no X Probably yes ○ Yes ○ Varies Don't know	We did not specifically look for studies evaluating drugs in this area	Infliximab has been widely implemented already. CLEAR regimen includes widely available antibiotics

SUMMARY OF JUDGEMENTS INFLIXIMAB

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

SUMMARY OF JUDGEMENTS THALIDOMIDE

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the compariso n	Probably favors the compariso n	**Does not favor either the interventio n or the comparison**	Probably favors the interventio n	Favors the interventio n	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No include d studies**
COST EFFECTIVENES S	Favors the compariso n	Probably favors the compariso n	Does not favor either the intervention or the comparison	Probably favors the interventio n	Favors the interventio n	Varies	**No include d studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varie s**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**

SUMMARY OF JUDGEMENTS GOLILMUMAB

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the compariso n	Probably favors the compariso n	**Does not favor either the interventio n or the comparison**	Probably favors the interventio n	Favors the interventio n	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No include d studies**
COST EFFECTIVENES S	Favors the compariso n	Probably favors the compariso n	Does not favor either the intervention or the comparison	Probably favors the interventio n	Favors the interventio n	Varies	**No include d studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varie s**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**

SUMMARY OF JUDGEMENTS USTEKINUMAB

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the compariso n	Probably favors the compariso n	**Does not favor either the interventio n or the comparison**	Probably favors the interventio n	Favors the interventio n	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No include d studies**
COST EFFECTIVENES S	Favors the compariso n	Probably favors the compariso n	Does not favor either the intervention or the comparison	Probably favors the interventio n	Favors the interventio n	Varies	**No include d studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varie s**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varie s**	**Don't know**
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**

SUMMARY OF JUDGEMENTS CLEAR

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the compariso n	Probably favors the compariso n	**Does not favor either the interventio n or the comparison**	Probably favors the interventio n	Favors the interventio n	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No include d studies**
COST EFFECTIVENES S	Favors the compariso n	Probably favors the compariso n	Does not favor either the intervention or the comparison	Probably favors the interventio n	Favors the interventio n	Varies	**No include d studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varie s**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION FOR INFLIXIMAB

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

1. In patients with chronic sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued active disease, we suggest the addition of infliximab compared to no additional therapy to reduce skin lesion desquamation. (Conditional recommendation, low quality of evidence).

3. We make no recommendations about the use of thalidomide, ustekinumab, golimumab, or the CLEAR regimen in the treatment of sarcoidosis due to limited evidence.

Justification

Two small, prospective, randomized, controlled studies demonstrate improvement in sarcoidosis cutaneous lesions as assessed by the SASI score with treatment by infliximab compared to continued glucocorticoids and other immunosuppressants alone in patients with cutaneous sarcoidosis. Infliximab is an immunomodulatory agent with a risk of adverse effects to include increased susceptibility to infection, though adverse events were low in the studies noted. The balance of effects would lead most patients to favor the use of infliximab. We make a conditional recommendation in favor of adding infliximab as it has been shown to improve some symptoms. However, due to the small number of studies, potential side effects, and cost of treatment, we make this a conditional recommendation.

Subgroup considerations

Patients with skin lesions may benefit from infliximab with reduction in lesion desquamation.

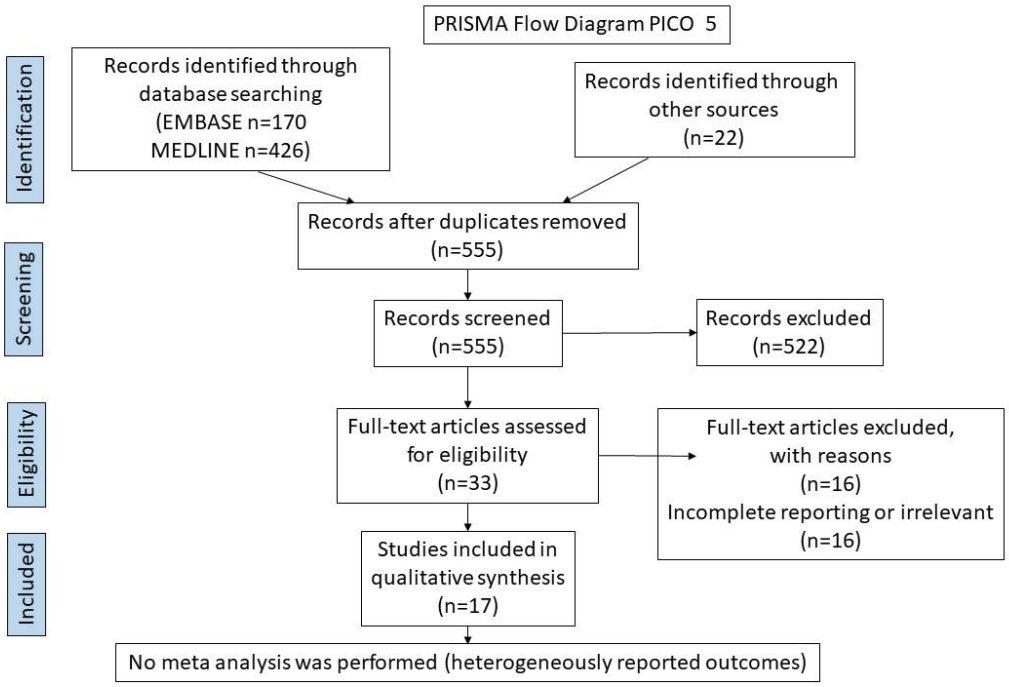
Implementation considerations

Barriers to implementation of treatment with infliximab include high treatment costs, the need for intravenous administration, and side effect related to immunomodulatory effects.

Research priorities

Further research is needed to confirm the effects of infliximab which have been noted in single studies, and to review the impact of the recommendation upon costs, resources, and health care equity.

PICO 5



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097; For more information, visit www.prisma-statement.org.

Evidence Summary PICO 5

Question: ***In patients with clinically relevant cardiac sarcoidosis, should glucocorticoids with or without other immunosuppressives versus no immunosuppression be used?***

Setting:

Bibliography: Nagai 2015 (32), Sperry 2017 (33), Nagai 2016 (34), Kato 2003 (35), Murtauh 2016 (36), Chapelon-Abric 2017 (37), Chapelon-Abric 2004 (38), Greulich 2013 (39), Moshen 2014 (40), Ise 2014 (41), Kudoh 2010 (42), Zhou 2017 (43), Kandolin 2015 (44), Kandolin 2015a (45), Nagano 2015 (46), Takaya 2014 (47), Yazaki 2001 (48)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppression	no immunosuppression	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppression	no immunosuppression	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Long-term adverse clinical outcome (with glucocorticoid therapy at diagnosis) (follow up: median 7.4 years; assessed with: All-cause death, symptomatic arrhythmia and heart failure requiring admission)												
1 (32) [32]	observational studies	not serious	not serious	serious [a]	serious [b]		67/83 (80.7%)	16/83 (19.3%)	**HR 0.41** (0.20 to 0.89)	**11 fewer per 100** (from 15 fewer to 2 fewer)	⨁◯◯ VERY LOW	CRITICAL
Long-term adverse clinical outcome (glucocorticoid therapy or immunosuppressant) (follow up: median 1.5 years; assessed with: All-cause death, treated ventricular tachycardia, heart failure requiring IV diuretics, heart transplantation)												
1 (33)	observational studies	not serious	not serious	serious [a]	serious [c]	none	60/83 (72.3%)	24/83 (28.9%)	**HR 0.69** (0.33 to 1.44)	**8 fewer per 100** (from 18 fewer to 10 more)	⨁◯◯ VERY LOW	CRITICAL
Cardiac death (with continuation of glucocorticoid therapy) (follow up: median 9.9 years; assessed with: Sudden cardiac death and death due to advanced heart failure))												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppression	no immunosuppression	Relative (95% CI)	Absolute (95% CI)		
2 (34; 35)	observational studies	Not serious	not serious	not serious	serious [d,e]	none	6/51 (11.8%)	7/25 (28.0%)	**RR 0.33** (0.12 to 0.86)	**19 fewer per 100** (from 25 fewer to 4 fewer)	⨁◯◯ VERY LOW	CRITICAL

Death or ventricular tachycardia (with current glucocorticoid use) (follow up: mean 3 years)

1 (36)	observational studies	Not serious	not serious	very serious [f]	serious [c]	none	5/23 (21.7%)	5/18 (27.8%)	**RR 0.78** (0.27 to 2.29)	**6 fewer per 100** (from 20 fewer to 36 more)	⨁◯◯◯ VERY LOW	CRITICAL

Complete and partial responders (glucocorticoids + immunosuppressant OR glucocorticoids alone) (follow up: median 60 months; assessed with: Absence of cardiac clinical symptoms and normalisation of ECG or imaging (complete); absence of cardiac clinical symptoms and persistence of abnormal heart imaging (partial)))

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppression	no immunosuppression	Relative (95% CI)	Absolute (95% CI)		
1 (37; 38)	observational studies	Not serious	not serious	serious [g]	serious [c]	none	Recovery rate 18/24 (75%) with glucocorticoids alone; 29/35 (83%) with glucocorticoids + IS (11/12 MTX, 17/20 CYC); glucocorticoids 39/41 (95.1%), rapid improvement in 31/39 (79.5%); additional IS in 11/39 (28.2%) including MTX, CYC, CsA. [i]				⨁◯◯◯ VERY LOW	CRITICAL

Relapse rate of cardiac sarcoidosis (follow up: median 19 months)

2 (37)	observational studies	Not serious	not serious	serious [g]	serious [c]	none	23/59 (39%) patients relapsed; relative risk in black patients 2.3, 95% CI 1-5; black female patients 3.0, 95% CI 1.1-8).				⨁◯◯◯ VERY LOW	CRITICAL

Cardiac death, aborted cardiac death or appropriate ICD shock (follow up: range 454 days to 1553 days)

2 (39; 40)	observational studies	Not serious	not serious	serious [g]	serious [g]	none	8/12 patients with hard endpoint received glucocorticoids only, none had additional immunosuppressives (ref 8). 4/12 patients with glucocorticoids, no change in LVEF (ref 9). [j]				⨁◯◯◯ VERY LOW	CRITICAL

Left ventricular parameters (follow up: mean 39 months; assessed with: MRI / Echocardiography / wash-out on SPECT)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppression	no immunosuppression	Relative (95% CI)	Absolute (95% CI)		
3 (35; 41-43)	observational studies	Not serious	not serious	very serious [j]	serious [g]	none	Improvement of LV parameters (LVED vol index, LVEF) only in small extent LGE patients; no difference before and after glucocorticoids in large extent LGE. Improvement in LVEF in pts treated with Glucocorticoids only. Washout on SPECT imaging as indirect measurement of LVEF improved in 10 patients 6 months after glucocorticoid therapy. LVEF improved significantly in 27 patients, in whom it was measured (total n=73 patients).				⨁◯◯◯ VERY LOW	CRITICAL

Improvement of cardiac troponins (follow up: median 17 months)

1 (44)	observational studies	Not serious	not serious	serious [j]	serious [g]	none	62 patients before and after measurements of cardiac troponins. Improvement with glucocorticoids reported at 12 months versus baseline.				⨁◯◯◯ VERY LOW	NOT IMPORTANT

Cardiac survival free of transplantation or aborted sudden cardiac death (follow up: range 12 months to 303 months)

1 (45)	observational studies	Not serious	not serious	serious [i]	serious [g]	none	102 patients received glucocorticoids (+ IS in 62 patients, 50 AZA, 6 MTX, 3 MMF, 2 CsA, 1 INF); 10-year probability of transplantation-free cardiac survival 83% total, 91% with immunosuppressive therapy.				⨁◯◯◯ VERY LOW	CRITICAL

Lack of AV-block improvement (follow up: range 8 months to 192 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppression	no immunosuppression	Relative (95% CI)	Absolute (95% CI)		
1 (35)	observational studies	Not serious	not serious	serious [g]	very serious [d]	none	3/7 (42.9%)	13/13 (100.0%)	**RR 0.45** (0.21 to 1.00)	**55 fewer per 100** (from 79 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Composite cardiac endpoint (follow up: median 5.1 years; assessed with: all-cause death, heart failure, symptomatic arrhythmia, appropriate ICD therapy, pacemaker requirement)

1 (43; 46)	observational studies	Not serious	not serious	serious [j]	serious [b]	none	HR 0.49 (0.21-1.21), p 0.13 for long-term adverse events with glucocorticoid therapy at the time of diagnosis. HR not significant for mortality related to immunosuppressive treatment.	⨁◯◯◯ VERY LOW	CRITICAL

Response to glucocorticoid treatment (assessed with: PET, Gallium scan)

1 (47)	observational studies	Not serious [l]	not serious	serious	serious [c]	none	Multivariate analysis identified female sex and high-grade degree heart block as predictive of glucocorticoid response (OR 16.0 (1.92–389) and 13.5 (1.92–279))	⨁◯◯◯ VERY LOW	CRITICAL

Long-term adverse clinical outcome (with glucocorticoid therapy at diagnosis) (follow up: range 1 months to 180 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppression	no immunosuppression	Relative (95% CI)	Absolute (95% CI)		
1 (48)	observational studies	Not serious	not serious	serious [i]	serious [c,d]	none	75/95 patients received glucocorticoids (20 autopsy cases). Outcome was better with GC therapy when LVEF was >50%, there was no difference between high-dose or lower dose GC therapy.				⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Composite outcome including results of different relative importance

b. A set of patients coming from same study protocol (46) followed during 5 years revealed that glucocorticoids therapy at diagnosis was not associated to a decrease of long-term adverse clinical outcomes in multivariate analysis: HR0.49 (95%CI 0.21 to 1.21)

c. Wide 95%CI pointing to important benefit or harm

d. Very low number of patients and events

e. Time to event data analysis reveals a statistically significant reduction of cardiac death (P=0.035, numerical data not shown)

f. Composite outcome including results of different relative importance and not all patients fulfilling the current guidelines definition of cardiac sarcoidosis

g. No direct comparison of treatment vs. no treatment (glucocorticoids and glucocorticoids + IS)

h. 2 pts did not receive glucocorticoids, no comparative results are given for these.

i. no comparative results

j. only glucocorticoids before and after, no direct comparison between treatment vs. no treatment

k. potential biases: selective outcome reporting, measurement of outcomes

Outcomes not assessed:

Quality of life: Important

Glucocorticoid sparing: Critical

Evidence to Decision Table PICO 5

QUESTION

Should glucocorticoids with or without other immunosuppressives versus no immunosuppression be used for patients with clinically relevant cardiac sarcoidosis?	
POPULATION:	patients with clinically relevant cardiac sarcoidosis
INTERVENTION:	immunosuppression
COMPARISON:	no immunosuppression
MAIN OUTCOMES:	Long-term adverse clinical outcome (with glucocorticoid therapy at diagnosis); Long-term adverse clinical outcome (glucocorticoid therapy or immunosuppressant); Cardiac death (with continuation of glucocorticoid therapy); Death or ventricular tachycardia (with current glucocorticoid use) ; Complete and partial responders (glucocorticoids + immunosuppressant OR glucocorticoids alone); Relapse rate of cardiac sarcoidosis; Cardiac death, aborted cardiac death or appropriate ICD shock ; Left ventricular parameters; Improvement of cardiac troponins; Cardiac survival free of transplantation or aborted sudden cardiac death; Lack of AV-block improvement; Composite cardiac endpoint; Response to glucocorticoid treatment; Long-term adverse clinical outcome (with glucocorticoid therapy at diagnosis);
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Cardiac sarcoidosis (CS), if left untreated, confers a high mortality rate, and patient care with CS requires interdisciplinary care by cardiologists, pulmonologists, and rheumatologists.	
Desirable Effects How substantial are the desirable anticipated effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Clinically important outcomes of therapy with glucocorticoids (GC) alone or in combination with immunosuppressives (IS) were addressed: All-cause death, symptomatic arrhythmia, heart failure requiring admission, and need for heart transplantation had hazard ratios ranging from 0.41 to 0.69 or risk ratios ranging from 0.33 to 0.79. Other studies, where numerical values were neither available nor deducible, also showed beneficial effects of GC therapy, alone or in combination with IS, in the majority of patients with CS. The main evidence was drive by GC therapy.	Direct effects of IS on CS cannot be inferred, as these were usually used in conjunction with GC therapy and there were no comparative studies.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large Moderate ○ Small ○ Trivial ○ Varies ○X Don't know	No information about side effects reported	While none of these studies routinely reported adverse events, the adverse events associated with GC and other immunosuppressives are well known and discussed elsewhere in this statement.

Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
X Very low Low ○ Moderate ○ High ○ No included studies	See evidence profiles. Overall, the certainty level of evidence is low as there was no RCT in CS and no direct comparisons of therapies.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	We found not studies specifically evaluation these drugs in this area.	Although there is no research evidence assessing how much people value the main outcomes, the current clinical practice considers that many patients value improved heart function and reduction of risk of sudden death as important. . A survey among sarcoidosis patients identified the quality of life and function mortality were important factors, with adverse events less important (9)
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	We found not studies specifically evaluation these drugs in this area.	In the opinion of the panel, the intervention probably favors the intervention since CS may have devastating consequences, including sudden cardiac death. However, the sufficient dose of GC therapy is currently unknown. Dose and duration of therapy require clinical judgement, and the addition of IS therapy is commonly used for prolonged therapy (longer than 1 year), which is required in many patients
Resources required		

How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	We found not studies specifically evaluation these drugs in this area.	Cost for GC are trivial, costs for IS therapies are moderate. In some patients, however, who may require biological therapies where costs can be increased. Overall, costs of treatments have to be balanced against potential healthcare benefits with avoidance of work loss, decreased rate of hospitalization, among others.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We found not studies specifically evaluation these drugs in this area.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	We found no studies specifically studying these drugs in this field.	
Equity What would be the impact on health equity?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	We found no studies specifically studying these drugs in this field.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We found no studies specifically studying these drugs in this field.	In the panelists experience, key stakeholders, such as patients and physicians do accept GC alone or in combination with IS. Insurance companies may be more reluctant to reimburse prescribing physicians since the evidence base is low.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	We found no studies specifically studying these drugs in this field.	In the panel memberss' experience, GC and/or IS therapy is feasible and currently in use. In addition, the medications used have a well-known risk profile.

SUMMARY OF JUDGEMENTS CARDIAC SARCOIDOSIS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably	**Yes**		Varie	Don't

	JUDGEMENT						
			yes			s	know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	**X**

CONCLUSIONS

Recommendation

For patients with evidence of functional cardiac abnormalities, including heart block, dysrhythmias, or cardiomyopathy, we recommend the use of glucocorticoids with or without other immunosuppressives (Strong recommendation, very low quality of evidence).

Justification

The level of evidence to support treatment approaches for cardiac sarcoidosis was very low, with multiple potential confounders and biases inherent in the available studies (49;50). Much of the data supporting the use of glucocorticoids is indirect, originating in association studies where glucocorticoid treatment is a covariate among other outcome predictors (49). There is likewise minimal description in the available studies of the indications for glucocorticoid treatment, or the characteristics of the treated vs untreated patients. The risk of death from cardiac sarcoidosis is high, especially for those with reduced left ventricular function (48). Since glucocorticoid treatment has been associated with improvement in left ventricular ejection (43;51), the task force members concluded that the danger associated with cardiac sarcoidosis favored glucocorticoid therapy for clinically relevant cardiac sarcoidosis (52;53). There was insufficient evidence to make a recommendation regarding other immunosuppressants, but we felt such treatment should still be considered to minimize toxicity of glucocorticosteroids. Figure 3 summarizes the approach used by most TF members.

Subgroup considerations

A clear-cut definition of "clinically relevant CS" does not exist. Usually, symptomatic patients or those with arrhythmias, evidence of heart failure are considered at-risk patients with a need for therapy, including immunosuppression.

Patients with lower left ventricular ejection fraction may be less responsive to immunosuppressive therapy. Therefore, the risk of adverse effects may justify a shorter period of treatment.

High-risk patients with a clear requirement of GC and IS have to be identified.

Implementation considerations

Immunosuppressive therapies for CS are currently in use by sarcoidosis specialists. Nevertheless, non-expert clinicians, including cardiologists, who may be the treating physicians, might not aware of the need for immunosuppressive therapy for CS in addition to device, ablation or antiarrhythmic therapy.

Monitoring and evaluation

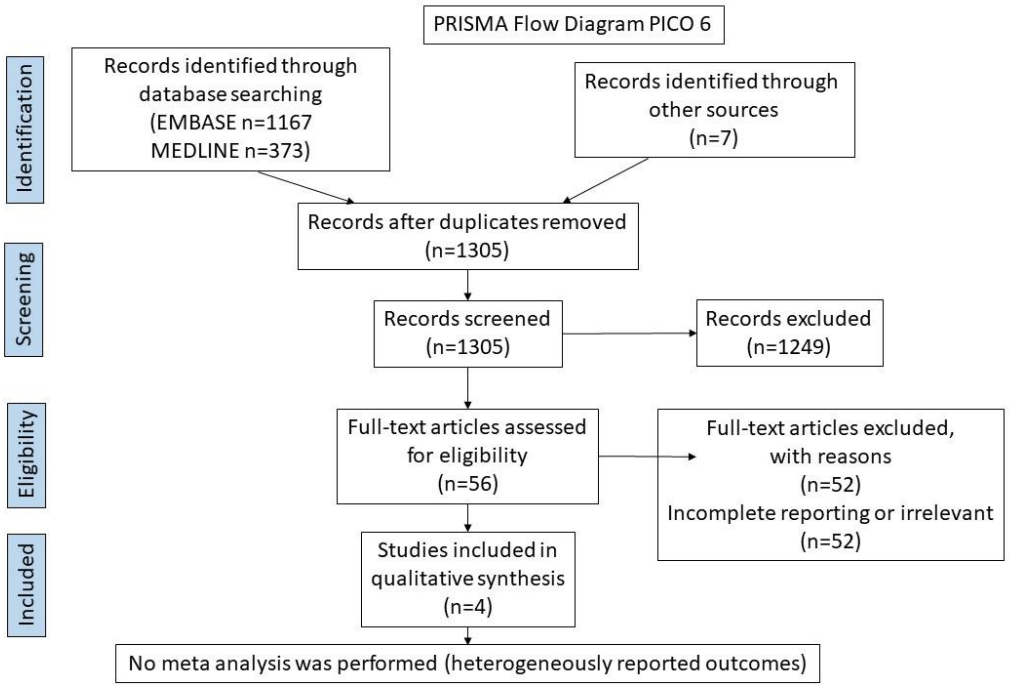
Patients with CS require careful monitoring by cardiologists and sarcoidosis specialists. Side-effects of therapies, including often prolonged glucocorticoid treatment, needs to be assessed regularly. Glucocorticoid-sparing agents may need to be used and the treatment response requires regular assessment, including the need for regular imaging techniques (echocardiography, PET scans, cardiac MRI).

Research priorities

The effects of non-glucocorticoidal therapies are currently not known and not based on conclusive trials. There is no compelling evidence to favor one agent over another.

Benefits/harms of ICD implantation and other devices should be assessed systematically in CS.

PICO 6



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097; For more information, visit www.prisma-statement.org.

Evidence Summary PICO 6

Author(s): Korsten

Question: ***In patients with neurosarcoidosis, should immunosuppressive treatment be used versus no immunosuppressive treatment?***

Setting: Outpatient

Bibliography: Joubert (54), Fritz (55), Bitoun (56), Gelfand (57),

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppressive treatment	no immunosuppressive treatment	Relative (95% CI)	Absolute (95% CI)		

Risk of ANY relapse with glucocorticoids (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppressive treatment	no immunosuppressive treatment	Relative (95% CI)	Absolute (95% CI)		
1 (54)	observational studies	not serious	not serious	serious [a]	not serious	none	85/254 (33.5%)	38/87 (43.7%)	**HR 0.59** (0.39 to 0.90)	**15 fewer per 100** (from 24 fewer to 3 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Risk of NEUROLOGICAL relapse with glucocorticoids (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

1 [1]	observational studies	not serious	not serious	serious [a]	serious [b]	none	58/254 (22.8%)	20/87 (23.0%)	**HR 0.68** (0.38 to 1.23)	**7 fewer per 100** (from 14 fewer to 4 more)	⨁◯◯◯ VERY LOW	CRITICAL

Risk of ANY relapse with Methotrexate (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

1 [1]	observational studies	not serious	not serious	serious [a]	not serious	none	44/125 (35.2%)	38/87 (43.7%)	not pooled	see comment	⨁◯◯◯ VERY LOW	CRITICAL

Risk of NEUROLOGICAL relapse with Methotrexate (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

1 [1]	observational studies	not serious	not serious	serious [a]	not serious	none	26/125 (20.8%)	20/87 (23.0%)	**HR 0.47** (0.25 to 0.87)	**11 fewer per 100** (from 17 fewer to 3 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Risk of ANY relapse with IV Cyclophosphamide (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

1 [1]	observational studies	not serious	not serious	serious [a]	not serious	none	11/120 (9.2%)	38/87 (43.7%)	**HR 0.18** (0.09 to 0.82)	**34 fewer per 100** (from 39 fewer to 6 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Risk of NEUROLOGICAL relapse with IV Cyclophosphamide (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

1 [1]	observational studies	not serious	not serious	serious [a]	not serious	none	10/120 (8.3%)	20/87 (23.0%)	**HR 0.26** (0.11 to 0.59)	**16 fewer per 100** (from 20 fewer to 9 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Risk of ANY relapse with Mycophenolate mofetil (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppressive treatment	no immunosuppressive treatment	Relative (95% CI)	Absolute (95% CI)		
1 [1]	observational studies	not serious	not serious	serious [a]	serious [b]	none	26/64 (40.6%)	38/87 (43.7%)	**HR 0.67** (0.37 to 1.23)	**12 fewer per 100** (from 25 fewer to 7 more)	⨁◯◯◯ VERY LOW	CRITICAL

Risk of NEUROLOGICAL relapse with Mycophenolate mofetil (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

1 [1]	observational studies	not serious	not serious	serious [a]	serious [b]	none	14/64 (21.9%)	20/87 (23.0%)	**HR 0.58** (0.25 to 1.34)	**9 fewer per 100** (from 17 fewer to 7 more)	⨁◯◯◯ VERY LOW	CRITICAL

Risk of ANY relapse with Infliximab (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

1 [1]	observational studies	not serious	not serious	serious [a]	not serious	none	4/28 (14.3%)	38/87 (43.7%)	**HR 0.31** (0.11 to 0.82)	**27 fewer per 100** (from 38 fewer to 6 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Risk of NEUROLOGICAL relapse with Infliximab (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

1 [1]	observational studies	not serious	not serious	serious [a]	serious [b]	none	1/28 (3.6%)	20/87 (23.0%)	**HR 0.160** (0.021 to 1.240)	**19 fewer per 100** (from 22 fewer to 5 more)	⨁◯◯◯ VERY LOW	CRITICAL

Risk of ANY relapse with Azathioprine (follow up: median 8 years; assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

1 [1]	observational studies	not serious	not serious	serious [a]	serious [b]	none	8/14 (57.1%)	38/87 (43.7%)	**HR 1.40** (0.55 to 3.53)	**12 more per 100** (from 17 fewer to 43 more)	⨁◯◯◯ VERY LOW	CRITICAL

Risk of NEUROLOGICAL relapse with Azathioprine (assessed with: signs, symptoms, imaging or pathological evidence if appropriate)

1 [1]	observational studies	not serious	not serious	serious [a]	serious [b]	none	6/14 (42.9%)	20/87 (23.0%)	**HR 1.88** (0.69 to 5.14)	**16 more per 100** (from 6 fewer to 51 more)	⨁◯◯◯ VERY LOW	CRITICAL

Favorable clinical outcome (follow up: median 4 years; assessed with: remission (complete or incomplete) and no need of alternative immunosuppressants)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppressive treatment	no immunosuppressive treatment	Relative (95% CI)	Absolute (95% CI)		
29 [2,c]	observational studies	not serious	not serious	serious [d]	serious [e]	none	First line therapy 161/227 (71%); Second line therapy 47/85 (55%); Third line therapy 7/18 (39%). Point estimate differences are: First vs second-line therapy: +16%; Second vs. third-line therapy: +16%; First vs. third-line therapy: +32%. [f]				⨁◯◯◯ VERY LOW	CRITICAL

Remission (follow up: median 4 years; assessed with: clinical symptoms: complete improvement without residual symptoms)

29 [2,c]	observational studies	not serious	not serious	serious [d,g]	serious [h]	none	Total remission was achieved in 126 out of 465 patients (27%, 95%CI 23-31%).			⨁◯◯◯ VERY LOW	CRITICAL

Incomplete remission (follow up: median 4 years)

29 [2,c]	observational studies	not serious	not serious	serious [d,g]	serious [h]	none	Incomplete remission was achieved in 147 out of 465 patients (32%, 95%CI 27-36%).			⨁◯◯◯ VERY LOW	IMPORTANT

Stable disease (follow up: median 4 years)

29 [2,c]	observational studies	serious [i]	not serious	serious [d,g]	serious [h]	none	Stable disease was achieved in 111 out of 465 patients (24%, 95%CI 20-28%).			⨁◯◯◯ VERY LOW	IMPORTANT

Deterioration (follow up: median 4 years)

29 [2,c]	observational studies	serious [i]	not serious	serious [d,g]	serious [h]	none	Stable disease was achieved in 28 out of 465 patients (6%, 95%CI 4-8%).			⨁◯◯◯ VERY LOW	IMPORTANT

Risk of NEUROLOGICAL relapse with Methotrexate plus glucocorticoids (follow up: median 12 months)

1 [3]	observational studies	not serious	not serious	very serious [d,h,j,k,l]	serious [h]	none	15/32 (46.8%) patients relapsed			⨁◯◯◯ VERY LOW	CRITICAL

Risk isk of NEUROLOGICAL relapse with Mycophenolate mofetil plus glucocorticoids (follow up: median 12 months) (follow up: median 12 months)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immunosuppressive treatment	no immunosuppressive treatment	Relative (95% CI)	Absolute (95% CI)		
1 [3]	observational studies	not serious	not serious	very serious [d,k]	serious [h]	none	11/14 (78.6%) patients relapsed				⨁◯◯◯ VERY LOW	CRITICAL

Favorable IMAGING response with Infliximab plus second-line and/or first-line therapy (assessed with: MRI)

1 [4]	observational studies	serious [m]	not serious	very serious [e,g,h,j,l]	serious [h]	none	46/56 (82.1%) with favorable imaging response; 45/58 (80.4%) with favorable clinical response				⨁◯◯◯ VERY LOW	NOT IMPORTANT

Adverse events

1 [1]	observational studies	not serious	not serious	very serious [d]	serious [h]	none	Obesity 32/234 (13.7%); osteoporosis 20/234 (8.5%); diabetes 13/234 (5.6%); tuberculosis 12/234 (5.1%), high blood pressure 8/234 (3.4%)				⨁◯◯◯ VERY LOW	

Adverse event - infections

3 [1,3,4]	observational studies	not serious	not serious	very serious [h]	serious [h]	none	Infections reported in 26/338 (7.7%) of patients				⨁◯◯◯ VERY LOW	

CI: Confidence interval; **HR:** Hazard Ratio

Explanations

a. The analysis is based on the association of the number of relapses and treatment sequences (numbers do not correspond to individual patients); method of imputation of events to treatment and non-treatment sequences is not clear; duration of treatment (or no treatment) periods is not known. The median duration of follow-up of the whole cohort is 8 years.

b. Wide 95%CI that includes a clinically meaningful benefit or harm

c. Based on 1 systematic review of case-series between 1980 and 2016 (Fritz et al.) including 29 studies. The specific number of patients ranged from 5-30 patients, median follow-up 13 yrs (range 3-31 yrs), varying data on a total number of 1088 patients.

d. Results have not been compared directly; Treatment effect has been obtained as an aggregated (not weighted) analysis from single-arm data.

e. First, second and third-line therapy effects cannot be compared statistically. Differences in point-estimates can be inferred but 95%CI is not available.

f. First-line: corticosteroid treatment; Second-line: immunossuppresive with methotrexate, azaqthioprine, mycophenolate mofetil, cyclosporine A or (hydroxil) chloroquine; Third-line: cyclophosphamide or immunomodulatoty medication (TNF-alpha inhibitors) or B-cell targeted therapy

g. Effect includes any treatment, however, over 80% of study patients received steroids

h. Differences between first, second, third-line therapies or no treatment are not known

i. Based on case series (Selection and reporting bias likely)

j. Second-line includes MTX, AZA, CsA, HCQ, CHQ, MMF

k. GC dose twice 40 mg (MTX) vs. 20 mg (MMF) group

l. Second-line treatment in the majority of patients

m. bias in measurement of outcome possible

QUESTION 6

In patients with neurosarcoidosis, should immunosuppressive treatment be used versus no immunosuppressive treatment??	
POPULATION:	neurosarcoidosis
INTERVENTION:	immunosuppressive treatment
COMPARISON:	no immunosuppressive treatment
MAIN OUTCOMES:	Risk of ANY relapse with glucocorticoids; Risk of NEUROLOGICAL relapse with glucocorticoids; Risk of ANY relapse with Methotrexate; Risk of NEUROLOGICAL relapse with Methotrexate; Risk of ANY relapse with IV Cyclophosphamide; Risk of NEUROLOGICAL relapse with IV Cyclophosphamide; Risk of ANY relapse with Mycophenolate mofetil; Risk of NEUROLOGICAL relapse with Mycophenolate mofetil; Risk of ANY relapse with Infliximab; Risk of NEUROLOGICAL relapse with Infliximab; Risk of ANY relapse with Azathioprine; Risk of NEUROLOGICAL relapse with Azathioprine; Favorable clinical outcome; Remission; Incomplete remission; Stable disease; Deterioration; Risk of NEUROLOGICAL relapse with Methotrexate plus glucocorticoids; Risk isk of NEUROLOGICAL relapse with Mycophenolate mofetil plus glucocorticoids (follow up: median 12 months); Favorable IMAGING response with Infliximab plus second-line and/or first-line therapy; Adverse events; Adverse event - infections;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	While there is no research evidence on organ-specific mortality in sarcoidosis, neurosarcoidosis confers a higher morbidity and mortality compared to other organ manifestations in sarcoidosis.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large	While the sample sizes in the included references were small, the adverse effects of GCs and other	

○ Varies ○ Don't know	immuosuppressive therapies are well known. In addition, a recent meta-analysis added substantial evidence for the risk of serious infections with biological therapies in rheumatoid arthritis with larger patient numbers (Singh et al. 2015). In this analysis, biological therapies at standard doses were associated with an OR 1.31 (95% credible interval [CrI] 1.09–1.58).	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	While the sample sizes in the included references were small, the adverse effects of GCs and other immuosuppressive therapies are well known. In addition, a recent meta-analysis added substantial evidence for the risk of serious infections with biological therapies in rheumatoid arthritis with larger patient numbers (Singh et al. 2015). In this analysis, biological therapies at standard doses were associated with an OR 1.31 (95% credible interval [CrI] 1.09–1.58).	The side-effects of glucocorticoids, immunosuppressives and bioloigcal therapies in general did not differ in sarcoidosis patients compared to their use for other conditions.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	There was a limited number of studies on the subject. There are numerous case reports with favorable effects of first-, second- and third-line therapies in neurosarcoidosis. One SLR and MA of case reports was included, and one large retrospective study	

–	was available for numeric analysis. There were two additional smaller retropsective studies. No randomized controlled trial specifically addressing neurosarcoidosis could be identified.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No relevant research evidence was identified.	The risk of any relapse, any neurological relapse and overall clinical outcome (favorable, partial response etc.) is probabyl equally important to all patients.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	While the overall evidence level for desirable effects is very low, neurosarcoidosis potentially leads to a large disease burden. The treatment interventions confer risks, especially associated with glucocorticoids and infectious complications but these are well-known and, in most cases, not serious. Also, with the advent of biosimilars, there is a substantial cost reduction, probably making third-line drugs more accessible to a larger number of patients.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	The costs associated with first-line and second-line therapies are low and can potentially save costs (avoidance of work loss, hospitatlization etc.). The costs for third-line therapies are high but these are used only in a limited subset of neurosarcoidosis patients. Also, biosimilars with reduced costs are available. However, these have not been studied in detail for their equivalence in neurosarcoidosis.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence was identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence was identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies	No research evidence was identified.	While there are no trials on this subject, there are subgroups of patients who are more severely affected by sarcoidosis, such as African-Americans. The effects of therapeutic interventions in these patients can either be higher due to an increased baseline severity or lower due to higher rate of treatment-refractory

○ Don't know		patients.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Patients and physicians are likely to accept immunosuppressive therapies. Many patients favor immunosuppressive therapies due to their GC sparing effects. Insurance companies are often reluctant to reimbursement of immunosuppressives becaus of limited evidence of efficacy. Biological therapies usually require individualized requests.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The intervention has been implemented into clinical practive. However, there are potential barriers to implement biological drugs for neurosarcoidosis due to their higher costs and limited evidence.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

For patients with clinically significant neurosarcoidosis, we suggest treatment with glucocorticoids (Strong recommendation, very low quality of evidence).

For patients with neurosarcoidosis that have been treated with glucocorticoids and have continued disease, we suggest the addition of methotrexate (conditional recommendation, very low quality of evidence).

For patients with neurosarcoidosis that have been treated with glucocorticoids and a second-line agent (methotrexate, azathioprine, mycophenolate mofetil) and have continued disease, we suggest the addition of infliximab (conditional recommendation, low quality of evidence).

Justification

The strong recommendation for glucocorticoids for clinically significant neurosarcoidosis is based on very low evidence, the committee felt the risk for significant irreversible neurologic loss warranted the strong recommendation. The conditional recommendation for infliximab was based on two retrospective studies (3;9) and other studies.

Subgroup considerations

Neurosarcoidosis can present heterogeneously with either CNS, peripheral, or spinal involvement. Based on the identified studies it is not possible to give specific recommendations for these differing manifestations. In clinical practice, however, the intensity of treatment will likely be guided by the severity of neurologic manifestations and potential inadvertent sequelae.

Implementation considerations

The use of immunosuppressive therapies has been widely adopted in neurosarcoidosis and most physicians are comfortable using glucocorticoids. The implementation of advanced treatment wit immunosuppressive therapies other than glucocorticoids may be restricted to centers familiar with their use and application in neurosarcoidosis. The use of biological therapies in neurosarcoidosis will likely be restricted to high-level care centers due to high costs and potential reimbursement issues.

Monitoring and evaluation

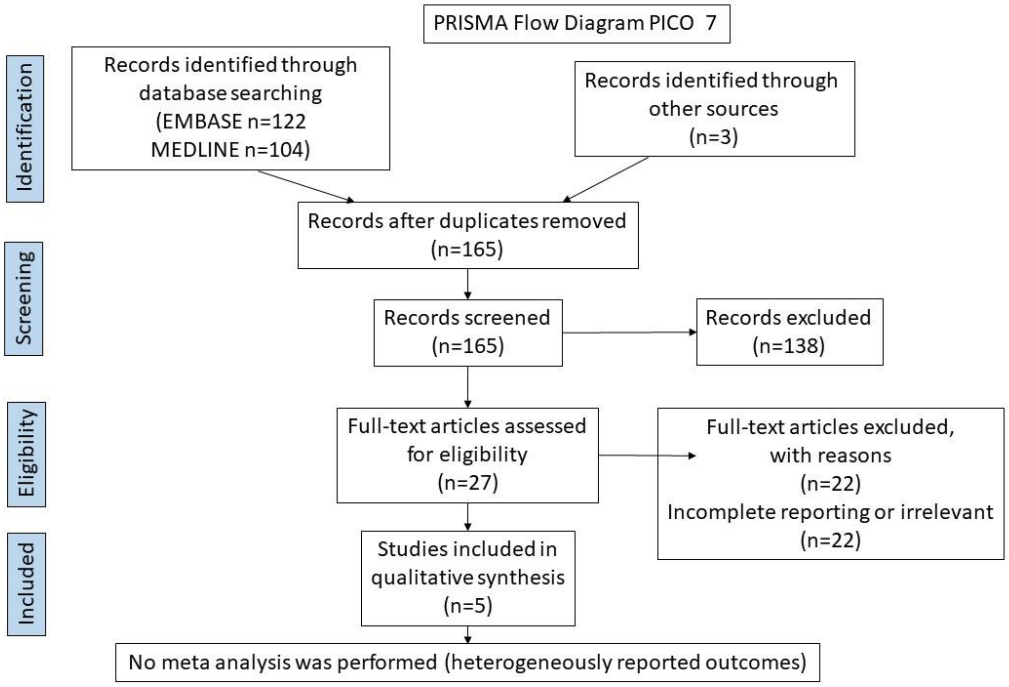
Patients with neurosarcoidosis require regular follow-up, most often with clinical and imaging techniques, such as cerebral magnetic resonance imaging. The use of glucocorticoids requires regular monitoring for expected side-effects, and more intense immunosuppressive therapies require frequent surveillance including laboratory

analyses and clinical assessment for efficacy.

Research priorities

Studies confirming the effectiveness of infliximab for neurosarcoidosis need to be performed. Studies examining whether high-dose corticosteroids are required with infliximab as initial therapy for advanced neurosarcoidosis may reduce the burden of corticosteroid toxicity. These studies would require standardized outcome measures. Given the relative rarity of neurosarcoidosis, multicenter studies will most likely be required. In addition, neurosarcoidosis may not be amenable to uniform treatment decisions but may require different treatments depending on the localization of affection (central, peripheral, spine).

PICO 7



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097; For more information, visit www.prisma-statement.org.

Cetainity of Assessment							Number of patients		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dexmethylphenidate 5 mg BID for 8 weeks**	**Placebo BID for 8 weeks**	**Median change (95% CI)**		
FVC before and after treatment											
1 (59)	randomised trials	Not serious	not serious	not serious	Very serious [2]	None	10	10	2.38 (1.17-4.53) pre to 2.56 (1.5-4.96) post for Rx; 2.38 (1.17-4.53 pre to 2.41 (1.5-4.65) post placebo	⊕⊕◯◯ Low	IMPORTANT

Cetainity of Assessment							Number of patients		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Armodafanil 150 mg x 4 weeks, 250 mg x 4 weeks**	**Placebo x 8 weeks (1 tab x 4 weeks then 2 x 4 weeks)**	**Median change (95% CI)**		
Fatigue assessment score, change from baseline											
1 (60)	randomised trials	Serious	not serious	not serious	Very serious [2]	None	15	15	-4.5 (-11-2.1) for Rx; 3.5 (0-8) for placebo	⊕⊕◯◯ Low	IMPORTANT
FACIT-F assessment score, change from baseline											

1	rando–mised trials	Serious	not serious	not serious	Very serious [2]	None	15	15	9 (-0.2-17) for Rx; -5 (-13-1.1) for placebo	⊕⊕◯◯ Low	IMPORTANT

Cetainity of Assessment							Number of patients		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Exercise program for 12 weeks**	**Control/ Usual care for 12 weeks**	**Median (Interquartile Range)**		
6MWT difference before and after intervention											
1 (61)	randomised trials	Not blinded	not serious	not	Very serious [1]		9	9	40 (31-62) for Int.; -20 (-63-14) for control	⊕◯◯◯ VERY LOW	IMPORTANT
Borg difference before and after intervention											
1	randomised trials	Not blinded	not serious	not	Very serious [1]		9	9	-1 (-4-0) for Int.; 0 (-1.5-1) for control	⊕◯◯◯ VERY LOW	IMPORTANT
MMRC difference before and after intervention											
1	randomised trials	Not blinded	not serious	not	Very serious [1]		9	9	-1 (-1.5-0) for Int.; 0 (0-0) for control	⊕◯◯◯ VERY LOW	IMPORTANT
Fatigue severity scale difference before and after intervention											
1	randomised trials	Not blinded	not serious	not	Very Serious [1]		9	9	-7 (-10-2) for Int.; 1 (0-4) for control	⊕◯◯◯	IMPORTANT

										VERY LOW	
Maximal inspiratory force difference before and after intervention											
1	randomised trials	Not blinded	not serious	not	Very Serious[1]		9	9	6 (2-24) for Int.; 6 (-12-6) for control	⨁◯◯◯ VERY LOW	IMPORTANT
Leg Strength difference before and after intervention											
1	randomised trials	Not blinded	not serious	not	Very Serious[1]		9	9	10 (5-17) for Int.; -4 (-6- -3) for control	⨁◯◯◯ VERY LOW	IMPORTANT
PaO2 difference before and after intervention											
1	randomised trials	Not blinded	not serious	not	Very Serious[1]		9	9	11 (1-17) for Int.; -2 (-5-9) for control	⨁◯◯◯ VERY LOW	IMPORTANT
SGRQ difference before and after intervention											
1	randomised trials		not serious	not	Very Serious[1]		9	9	-19 (-25-1) for Int.; -11 (-12-2) for control		IMPORTANT

PICO 7

Date 9/7/2018

Question: ***In patients with sarcoidosis associated fatigue, should immunosuppressive, , neurostimulants, exercise, or other treatments be used versus no treatment for fatigue?***

Setting: Outpatient

Bibliography: Karadall1 2016 (58), Lower 2008 (59), Lower 2013 (60), Naz 2018 (61)

Quality of Assessment							Number of Lesions		Effect	Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Inspiratory muscle training for 6 weeks**	**Sham training for 6 weeks**		**Mean (95% CI)**		
6MWT difference following intervention												
1 (58)	randomised trials	Not serious	not serious	n serio ous t	Serious[2]	None	15	15		66.1 (44.3-88.0) for Rx; 11.6 (-10.2-33) for sham	⊕⊕◯◯ Low	IMPORTANT
Shuttle walk test difference following intervention												
1	randomised trials	Not serious	not serious	n serio ous t	Serious[2]	None	9	9		61.7 (31.0-91.2) for Rx; 16.2 (-14.5-46) for sham	⊕⊕◯◯ Low	IMPORTANT
Difference in Borg dyspnea scale following intervention												
1	randomised trials	Not serious	not serious	n serio ous t	Serious[2]	None	9	9		-1.0 (-1.7- -0.4) for Rx; 0.1 (-0.6-0.8) for sham	⊕⊕◯◯ Low	IMPORTANT
Difference in maximal inspiratory pressure following intervention												
1	randomised trials	Not serious	not serious	n serio ous t	Serious[2]	None	9	9		45.9 (39.3-52.6) for Rx; 14.4 (7.7-21.1) for sham	⊕⊕◯◯ Low	IMPORTANT
Difference in maximal expiratory pressure following intervention												
1	randomised trials	Not serious	not serious	n serio ous t	Serious[2]	None	9	9		49.7 (39.3-60.2) for Rx; 21.7 (11.2-32.2) for	⊕⊕◯◯ Low	IMPORTANT

										sham		
Difference in MMRC following intervention												
1	randomised trials	Not serious	not serious	n serious t	Serious[2]	None	9	9		-1.1 (-1.3- -0.8) for Rx; -0.7 (-15.4- -3.8) for sham	⊕⊕◯◯ Low	IMPORTANT

Quality of Assessment	Number of Lesions	Effect	Quality	Importance

№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dexmethylpheniadate 5 mg BID for 8 weeks**	**Placebo BID for 8 weeks**		**Median (Range)**		
FVC before and after treatment												
1 (59)	randomised trials	Not serious	not serious	n serious t	Very serious[2]	None	10	10		2.38 (1.17-4.53) pre to 2.56 (1.5-4.96) post for Rx; 2.38 (1.17-4.53 pre to 2.41 (1.5-4.65) post placebo	⊕⊕◯◯ Low	IMPORTANT

Quality of Assessment	Number of Lesions	Effect	Quality	Importance

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Armodafanil 150 mg x 4 weeks, 250 mg x 4 weeks	Placebo x 8 weeks (1 tab x 4 weeks then 2 x 4 weeks)		Median change (95% CI)		
Fatigue assessment score, change from baseline												
1 (60)	randomised trials	Serious	not serious	n serio ous t	Very serious[1]	None	15	15		-4.5 (-11-2.1) for Rx; 3.5 (0-8) for placebo	⊕⊕◯◯ Low	IMPORTANT
FACIT-F assessment score, change from baseline												
1	randomised trials	Serious	not serious	n serio ous t	Very serious[1]	None	15	15	**0.004**	9 (-0.2-17) for Rx; -5 (-13-1.1) for placebo	⊕⊕◯◯ Low	IMPORTANT

Quality of Assessment	Number of Lesions	Effect	Quality	Importance

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise program for 12 weeks	Control/ Usual care for 12 weeks		Median (Inter		

										quartile Range)		
6MWT difference before and after intervention												
1 (61)	randomised trials	Not blinded	not serious	n serious	Very serious[1]		9	9		40 (31-62) for Int.; -20 (-63-14) for control	⊕◯◯◯ VERY LOW	IMPORTANT
Borg difference before and after intervention												
1	randomised trials	Not blinded	not serious	n serious	Very serious[1]		9	9		-1 (-4-0) for Int.; 0 (-1.5-1) for control	⊕◯◯◯ VERY LOW	IMPORTANT
MMRC difference before and after intervention												
1	randomised trials	Not blinded	not serious	n serious	Very serious[1]		9	9		-1 (-1.5-0) for Int.; 0 (0-0) for control	⊕◯◯◯ VERY LOW	IMPORTANT
Fatigue severity scale difference before and after intervention												
1	randomised trials	Not blinded	not serious	n serious	Very Serious[1]		9	9		-7 (-10-2) for Int.; 1 (0-4) for control	⊕◯◯◯ VERY LOW	IMPORTANT
Maximal inspiratory force difference before and after intervention												
1	randomised trials	Not blinded	not serious	n serious	Very Serious[1]		9	9		6 (2-24) for Int.; 6 (-12-6) for control	⊕◯◯◯ VERY LOW	IMPORTANT
Leg Strength difference before and after intervention												
1	randomised trials	Not blinded	not serious	n serious	Very Serious[1]		9	9		10 (5-17) for Int.; -4 (-6- -3) for control	⊕◯◯◯ VERY LOW	IMPORTANT
PaO2 difference before and after intervention												
1	randomised trials	Not blinded	not serious	n serious	Very Serious[1]		9	9		11 (1-17) for Int.; -2 (-5-9) for control	⊕◯◯◯ VERY LOW	IMPORTANT

SGRQ difference before and after intervention												
1	randomised trials	Not blinded	not serious	n serio ous t	Very Serious[1]		9	9		-19 (-25-1) for Int.; -11 (-12-2) for control		IMPORTANT

1. Very Small number of events and patients

Outcomes not assessed:

Adverse events: Critical

PICO Question: Question 7a

QUESTION

POPULATION:	Patients with chronic sarcoidosis and fatigue
INTERVENTION:	Inspiratory muscle training for 6 weeks
COMPARISON:	Sham treatment

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Compared to those doing sham training, six weeks of inspiratory muscle training led to improvement in six minute walk test P<0.001), dyspnea (P<0.05), maximal inspiratory and expiratory pressure (P<0.001), and symptoms as measured by MMRC score (58). Fatigue significantly reduced as measured with the Fatigue Severity Scale.**	A specific inspiratory training program was used in a small group of patients. Did not measure the FAS. No significant improvement in pulmonary function testing, including FVC.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Reported that all patients tolerated inspiratory muscle training without complaints and no adverse reactions occurred.**	

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Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
X Very low Low ○Moderate ○ High ○ No included studies		There is a single prospective controlled trial with nine patients in each arm which limits precision.

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		No adverse events reported during the study and the risk of undesirable effects seems very low.

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**No specific studies were identified to answer this question**	A questionnaire perfomed by ELF identified improvement in quality fo life, including reduction of fatigue, were high priority (9)..
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	No specific studies were identified to answer this question	Requires some training for patient

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Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No specific studies were identified to answer this question	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No specific studies were identified to answer this question	Fairly inexpensive modality
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No specific studies were identified to answer this question	Widely available

SUMMARY OF JUDGEMENTS INSPIRATORY MUSCLE TRAINING

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Very Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably	Probably	Yes		Varie	**Don't**

	JUDGEMENT						
		no	yes			s	know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION FOR INSPIRATORY MUSCLE TRAINING

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In patients with sarcoidosis who have troublesome fatigue, we suggest a pulmonary rehabilitation program and/or inspiratory muscle strength training for 6-12 weeks to improve fatigue. (Conditional recommendation, very low quality of evidence).

Justification

Inspiratory muscle training for 6-12 weeks was recommended on the basis on current evidence. The inspiratory muscle training is inexpensive and should be readily available. A conditional recommendation was made because there have been no confirmatory studies.

Subgroup considerations

Applies to patients with chronic sarcoidosis and fatigue.

Implementation considerations

Results could vary based on the inspiratory muscle training protocol.

Research priorities

Further research is needed to confirm the effects of inspiratory muscle training which have been noted in a single study, and to review the impact of the recommendation upon costs, resources, and health care equity. The effects of long term inspiratory muscle training should be explored.

PICO Question: Question 7b

QUESTION

POPULATION:	Patients with chronic sarcoidosis and fatigue
INTERVENTION:	Dexmethylphenidate 5 mg BID for 8 weeks
COMPARISON:	Placebo

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Compared to placebo, improved forced vital capacity with dexmethylphenidate ($p<0.01$). Also significant improvement in FAS ($P<0.02$) and FACIT-F ($P<0.001$). Significant improvement in SGRQ symptoms ($P<0.02$), but not SGRQ total (59)	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**Dexmethylphenidate:** No patient discontinued drug due to toxicity, but four reduced afternoon dose (59). Insomnia rated equally during active drug and placebo, but precise metrics are not available.	Data exists concerning adverse effects of dexmethylphenidate from other populations including insomnia.

Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies		One small prospective trial of 10 patients in each treatment arm is available. The size of the study implicates precision.

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Dexmethylphenidate** ● Probably favors the intervention	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**No specific studies were identified to answer this question.**	In survey of sarcoidosis patients, overall improvement of quality of life was highest priority (9).
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies X Don't know	No specific studies were identified to answer this question	Several versions of methylphenidate are available.

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Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased Varies X Don't know	No specific studies were identified to answer this question	Equity may be implicated in a fashion determined by prescription coverage.

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no Probably yes ○ Yes ○ Varies X Don't know	No specific studies were identified to answer this question	While drug is widely available,it is generally handled as a controlled substance because of potential addiction.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question	Drug is widely available

SUMMARY OF JUDGEMENTS D-METHYLPHENIDATE

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION FOR DEXMETHYLPHENIDATE

Strong	Conditional	Conditional	Conditional	Strong

recommendation against the intervention	recommendation against the intervention	recommendation for either the intervention or the comparison	recommendation for the intervention	recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In patients with sarcoidosis who have troublesome fatigue that is not related to disease activity, and after consideration of a pulmonary exercise or rehabilitation program, we suggest the use of d-methylphenidate for 8 weeks to tests its effect on fatigue and tolerability (Conditional recommendation, low quality of evidence).

Justification

Based on one prospective, randomized, controlled study demonstrating improvement in fatigue, quality of life and forced vital capacity when dexmethylphenidate was used compared to placebo. The recommendation was conditional because this was a single trial with no further confirmation for this agent.

Subgroup considerations

The recommendation applies to a subgroup of chronic sarcoidosis patients with fatigue.

Implementation considerations

Barriers to implementation of treatment with dexmethylphenidate include modest treatment costs and the side-effect of insomnia.

Research priorities

Further research is needed to confirm the effects of dexmethylphenidate which has been noted in a single study, and to review the impact of the recommendation upon costs, resources, and health care equity. The effects of the use of dexmethylphenidate long term should be explored.

PICO Question: Question 7c

QUESTION

POPULATION:	Patients with chronic sarcoidosis and fatigue
INTERVENTION:	Armodafanil 150 mg daily for four weeks, then 250 mg daily for four weeks
COMPARISON:	Placebo

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Compared to placebo arm, when on armodafinil there was a significant improvement in fatigue as measured by the FAS (P<0.05) and the FACIT-F score (P<0.02) and short form-36 vitality (P<0.01) (60). No difference in FVC, SGRQ, or sarcoidosis health questionnaire.	Improvement noted for those with or without hypersomnulance as assessed using mean sleep latency time,

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	One patient (7%) discontinued active treatment due to anxiety.	The adverse effects of armodafanil are also known from data in other patient populations.

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Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ●Low ○ Moderate ○ High ○ No included studies		One small prospective trial of 15 patients in each treatment arm is available. The size of the study implicates precision.

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Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Armodafanil** Probably favors the intervention	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	No specific studies were identified to answer this question	Fatigue is an important patient-focused outcome. In a survey of sarcoidosis patients, improvement of quality of life was the highest priority (9).
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No specific studies were identified to answer this question	Armodafinil and modafinil are widely available.

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No specific studies were identified to answer this question	Equity may be implicated in a fashion determined by prescription coverage.

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question	Drug is widely available
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No specific studies were identified to answer this question	Drug is widely available

SUMMARY OF JUDGEMENTS: ARMODAFINIL

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION FOR ARMODAFANIL

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In patients with sarcoidosis who have troublesome fatigue that is not related to disease activity, and after consideration of a pulmonary exercise or rehabilitation program, we suggest the use of armodafanil for 8 weeks to tests its effect on fatigue and tolerability. (Conditional recommendation, low quality of evidence).

Justification

Based on one prospective, randomized, controlled study demonstrated improvement in fatigue when armodafanil was used compared to placebo, there was a conditional recommendation to cosider this therapy. There have been no cofirmative studies with this agent.

Subgroup considerations

The recommendation applies to a subgroup of chronic sarcoidosis patients with fatigue.

Implementation considerations

Barriers to implementation of treatment with armodafanil include modest treatment costs.

Research priorities

Further research is needed to confirm the effects of armodafanil which has been noted in a single study, and to review the impact of the recommendation upon costs, resources, and health care equity. The effects of long term use of armodafanil should be explored.

PICO Question: Question 7d

QUESTION

POPULATION:	Patients with chronic sarcoidosis and fatigue
INTERVENTION:	Exercise program for 12 weeks
COMPARISON:	Usual care

ASSESSMENT

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Compared to group randomized to usual care, those who participated in a 12 week exercise program, had a median 40 m increase in six minute walk distance (P<0.05), quality of life and less dyspnea (P<0.05) and less fatigue assessed using the fatigue severity score (P<0.001) (61).	A specific exercise program was used in a small group of patients. Control group were those who chose not to participate in program.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		There was no comment on how frequently patients enrolled in supervised training and subsequently discontinued training. In general, supervised training is well tolerated.

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Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
X **Very low** Low ○ Moderate ○ High ○ No included studies		There is a single prospective controlled trial with nine patients in each arm. The study was not blinded. Choosing to study all those who decided to participate in exercise program may have biased results. This limits the certainty of the evidence.

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Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Not specifically addressed in this study, but the risk of undesirable effects seems very low.

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	No specific studies were identified to answer this question	Improvement in respiratory physiology, exercise tolerance, and quality of life is likely to be highly valued by patients.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	No specific studies were identified to answer this question	Many programs will have pulmonary rehabilitation facilities.

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No specific studies were identified to answer this question	In some parts of world, structured physical training is moderately expensive.

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No specific studies were identified to answer this question	Pulmonary rehabilitation may not be covered by insurance.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No specific studies were identified to answer this question	Pulmonary rehabilitation facilities are available in most areas, but are often hospital based.

SUMMARY OF JUDGEMENTS: EXERCISE PROGRAM

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Very Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**

TYPE OF RECOMMENDATION FOR EXERCISE TRAINING

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In patients with sarcoidosis and no contraindications who have troublesome fatigue, we suggest a pulmonary rehabilitation program for 6-12 weeks to improve fatigue. (Conditional recommendation, very low quality of evidence).

Justification

There was one small prospective study demonstrating improvement in six minute walk distance, perception of dyspnea, and fatigue for those who participated in supervised training compared to no specific therapy. This observation has been confrimed by subsequent open label studies. The recommendation was conditional because the small number of patients studied.

Subgroup considerations

Patients with chronic sarcoidosis and fatigue.

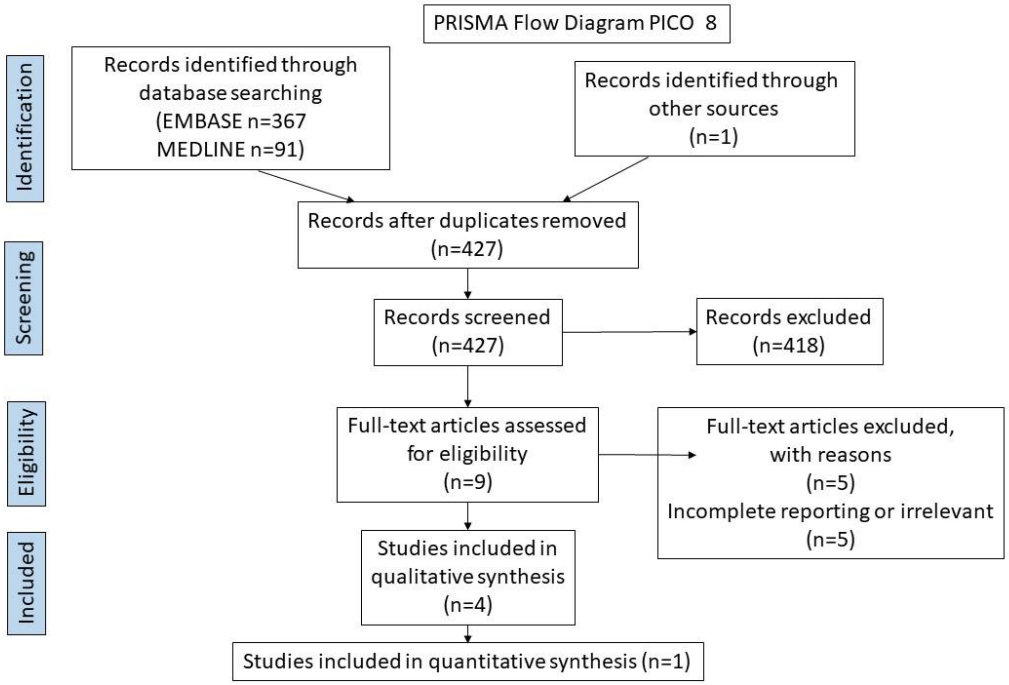
Implementation considerations

Results could vary based on the specific exercise training protocol.

Research priorities

Further research is needed to confirm the effects of exercise training which have been noted in a single study, and to review the impact of the recommendation upon costs, resources, and health care equity. The effects of long term exercise training should be explored.

PICO 8



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097; For more information, visit www.prisma-statement.org.

Evidence tables PICO 8

Question: ***In sarcoidosis patients with small fiber neuropathy, should immunosuppressants or intravenous immunoglobulin be prescribed versus no treatment?*** **Bibliography**: Tavee 2017

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIg	no treatment (receiving analgesics and glucocorticoids and/or methotrexate)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIg	no treatment (receiving analgesics and glucocorticoids and/or methotrexate)	Relative (95% CI)	Absolute (95% CI)		
Clinical Improvement (follow up: 31 months)												
1	observational studies (62)	very serious[a]	not serious	not serious	serious	none	47/62 (75.8%)	4/27 (14.8%)	**RR 5.12** (2.05 to 12.78)	**610 more per 1,000** (from 156 more to 1,000 more)	⨁⨁◯◯ VERY LOW	IMPORTANT
Clinical deterioration (follow up: 31 months)												
1	observational studies (62)	very serious[a]	not serious	not serious	serious	none	6/62 (9.7%)	21/27 (77.8%)	**RR 0.12** (0.06 to 0.27)	**684 fewer per 1,000** (from 731 fewer to 568 fewer)	⨁⨁◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Bias due to confounding, measurement of outcomes and selection of the reporting results.

Question: Anti-TNFa compared to no treatment (receiving analgesics and glucocorticoids and/or methotrexate) for small fiber neuropathy in sarcoidosis

Bibliography: Tavee 2017

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anti-TNFa	no treatment (receiving analgesics and glucocorticoids and/or methotrexate)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Clinical Improvement (follow up: 31 months)												
1	observational studies	very serious[a]	not serious	not serious	serious	none	8/12 (66.7%)	4/27 (14.8%)	**RR 4.50** (1.67 to 12.10)	**519 more per 1,000** (from 99 more to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Clinical deterioration (follow up: 31 months)												
1	observational studies	very serious[a]	not serious	not serious	serious	none	3/12 (25.0%)	21/27 (77.8%)	**RR 0.32** (0.12 to 0.87)	**529 fewer per 1,000** (from 684 fewer to 101 fewer)	⨁◯◯◯ VERY LOW	IMPORTANTT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Bias due to confounding, measurement of outcomes and selection of the reporting results.

Question: IVIg + Anti-TNFa compared to no treatment (receiving analgesics and glucocorticoids and/or methotrexate) for small fiber neuropathy in sarcoidosis

Bibliography: Tavee 2017

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIg + Anti-TNFa	no treatment (receiving analgesics and glucocorticoids and/or methotrexate)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Clinical Improvement (follow up: 31 months)												
1	observational studies	very serious[a]	not serious	not serious	serious	none	10/14 (71.4%)	4/27 (14.8%)	**RR 4.82** (1.84 to 12.63)	**566 more per 1,000** (from 124 more to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Clinical deterioration (follow up: 31 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIg + Anti-TNFa	no treatment (receiving analgesics and glucocorticoids and/or methotrexate)	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	very serious[a]	not serious	not serious	serious	none	2/14 (14.3%)	21/27 (77.8%)	**RR 0.18** (0.05 to 0.67)	**638 fewer per 1,000** (from 739 fewer to 257 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Bias due to confounding, measurement of outcomes and selection of the reporting results.

Outcomes no assessed:

Adverse events: Critical

ETD PICO 8

QUESTION

POPULATION:	Sarcoidosis patients with severe small fiber neuropathy deemed to be caused by sarcoidosis
INTERVENTION:	Intravenous immunoglobulin (IVIG), anti-tumor necrosis factor (anti-TNF) (62)
COMPARISON:	Placebo or no treatment

ASSESSMENT

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial X Small ○ Moderate ○ Large ○ Varies ○ Don't know	**IVIG (62):** An observational study involving 143 patients with small fiber neuropathy caused by sarcoidosis evaluated IVIG and anti-TNFa (infliximab) versus glucocorticoids and/or methotrexate. They evaluated treatment response as perceived by patients. More patients receiving IVIG (RR 5.12 [2.05-12.78]) experienced an improvement in their symptoms compared to “no treatment”. Also, significantly higher proportion of the patients receiving “no treatment” experience a deterioration, compared to IVIG (RR imm0.12 [0.06-0.27]).	
○ Trivial X Small ○ Moderate ○ Large ○ Varies ○ Don't know	**anti-TNFa (62):** An observational study involving 143 patients with small fiber neuropathy caused by sarcoidosis evaluated IVIG and anti-TNFa	

–	(infliximab) versus glucocorticoids and/or methotrexate. They evaluated treatment response as perceived by patients. More patients receiving anti-TNFa (RR 4.5 [1.67-12.10]) experienced an improvement in their symptoms compared to "no treatment". Also, significantly higher proportion of the patients receiving "no treatment" experience a deterioration, compared to anti-TNFa (RR 0.32 [0.12-0.87]).	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large X Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**IVIG:** No direct data from patients with sarcoidosis and small fiber neuropathy. However, there is ample indirect data from other patient groups.	
○ Large X Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**anti-TNFa:** No direct data from patients with sarcoidosis and small fiber neuropathy. However, there is ample indirect data from other patient groups.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **Very low** ○ Low ○ Moderate ○ High ○ No included studies	**IVIG: See evidence profiles and section summary**	Study that evaluated IVIg was an observational study. In addition, no SFN specific endpoint was evaluated in all patients in this study.

• **Very low** ○ Low ○ Moderate ○ High ○ No included studies	**Anti-TNF: See evidence profiles and section summary**	Study that evaluated anti-TNFa was an observational study. In addition, no SFN specific endpoint was evaluated in all patients in this study.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison X Probably favors the intervention ○ Favors the intervention ○ Varies Don't know	**IV Ig:**The study populations were very limited and therefore, we could not draw a safe conclusion regarding the balance between desirable and undesirable effects for SFN. However intervention widely used in other conditions with minimal complications.	
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison X Probably favors the intervention ○ Favors the intervention ○ Varies Don't know	**Anti-TNF**: The study populations were very limited and therefore, we could not draw a safe conclusion regarding the balance between desirable and undesirable effects for SFN. However, anti-TNF widely used for sarcoidosis and other considerations with minimal complications.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability	**IVIG: No specific studies were identified to answer this question.**	Although there is no research evidence assessing how much people value the main outcomes, from the current clinical practice GDG considers that patients value avoidance of pain. In survey of sarcoidosis patients, overall improvement of quality of

• Probably no important uncertainty or variability _ ○ No important uncertainty or variability ○ No known undesirable outcomes		life was highest priority (9).
○ Important uncertainty or variability ○ Possibly important uncertainty or variability • Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**Anti-TNF: No specific studies were identified to answer this question.**	Although there is no research evidence assessing how much people value the main outcomes, from the current clinical practice GDG considers that patients value avoidance of pain. In survey of sarcoidosis patients, overall improvement of quality of life was highest priority (9).
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**IV Ig: No specific studies were identified to answer this question.**	IV Ig: expensive and requires infusion center
• Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Anti-TNF: No specific studies were identified to answer this question.**	Anti-TNFa: expensive and requires an infusion center
Equity		

What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased • Increased ○ Varies ○ Don't know	**IV Ig: No specific studies were identified to answer this question.**	This treatment is expensive and may not be available in less affluent countries
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased • Increased ○ Varies ○ Don't know	**Anti-TNF No specific studies were identified to answer this question.**	This treatment is expensive and may not be available in less affluent countries
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No Probably no ○ Probably yes ○ Yes X Varies ○ Don't know	**IV Ig: No specific studies were identified to answer this question.**	There are significant costs associated with treatment.
○ No Probably no ○ Probably yes ○ Yes X Varies ○ Don't know	**No specific studies were identified to answer this question.**	There are significant costs associated with treatment
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no • Probably yes ○ Yes ○ Varies	**No specific studies were identified to answer this question.**	Such treatments would require close monitoring of the patient by clinical experts. That would generally be feasible if the clinical effectiveness was confirmed.

○ Don't know		
○ No ○ Probably no • Probably yes ○ Yes ○ Varies ○ Don't know	**No specific studies were identified to answer this question.**	Such treatments would require close monitoring of the patient by clinical experts. That would generally be feasible if the clinical effectiveness was confirmed.

SUMMARY OF JUDGEMENTS IVIG

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

SUMMARY OF JUDGEMENTS ANTI-TNF

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION: RESEARCH RECOMMENDATION

WE MAKE NO RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Inadequate data is available regarding the safety and clinical effectiveness of immunosuppressives for patients with sarcoidosis and small fiber neuropathy. We recommend conducting high quality clinical trials to further evaluate such interventions. We could not make a recommendation regarding cibinetide because it is not commercially available.

Justification

Cibinetide, IVIG and anti-TNFa appear to have beneficial effects for patients with sarcoidosis and small fiber neuropathy. Cibinetide appears to increase the abundance of small nerve fibers in the cornea and the skin, improve the results of the small fiber neuropathy screening, autonomic symptoms, fiber neuropathy symptoms and related pain, quality of life and 6-MWT. IVIG and anti-TNFa appear to be associated with an increase in the proportion of patients experiencing an improvement in their symptoms. However, all three interventions are also associated with adverse events and the panel believes that the balance between benefits and risks should be further evaluated in rigorous clinical trials before recommending these treatments for routine care.

Subgroup considerations

Not applicable

Implementation considerations

Not applicable

Research priorities

- Safety and clinical effectiveness of cibinetide, IVIG, anti-TNFa and other interventions for patients with sarcoidosis and small fiber neuropathy.

- Development and clinical validation of accurate biomarkers and/or clinical scores to assess treatment response.

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