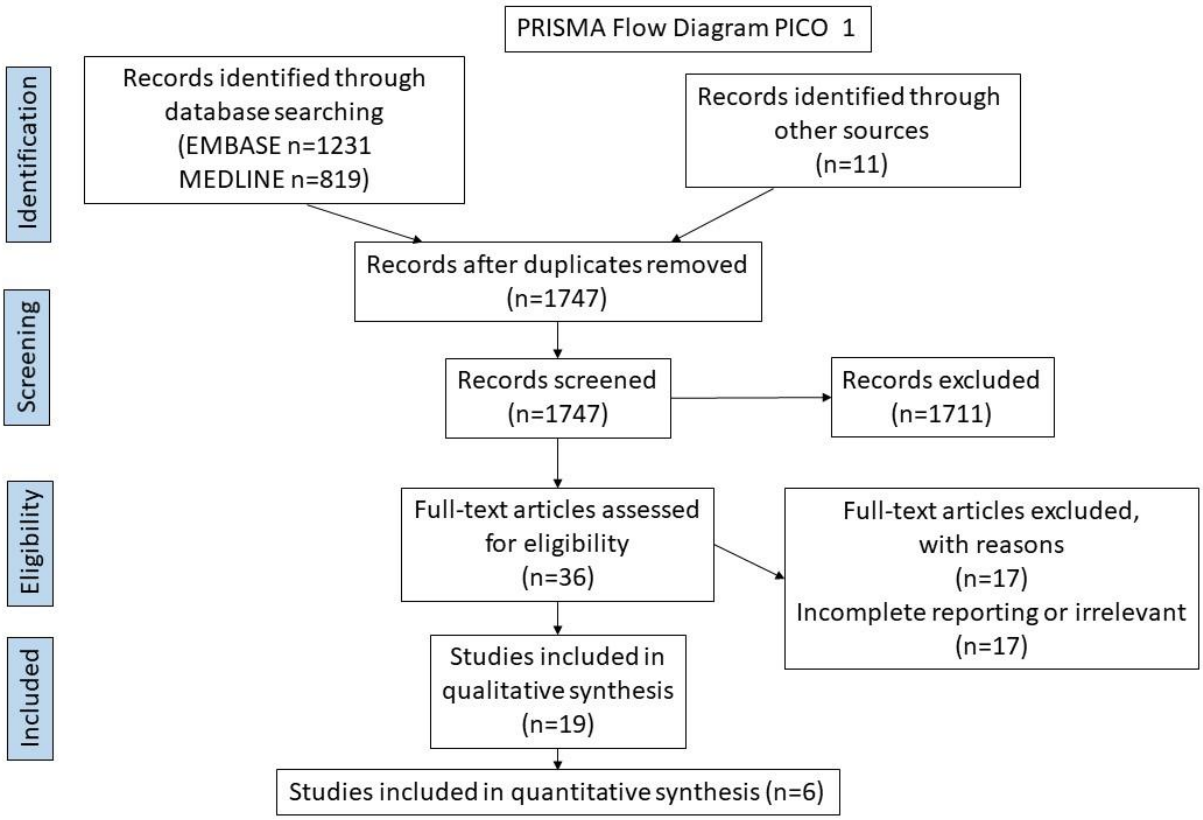
Supplement 2

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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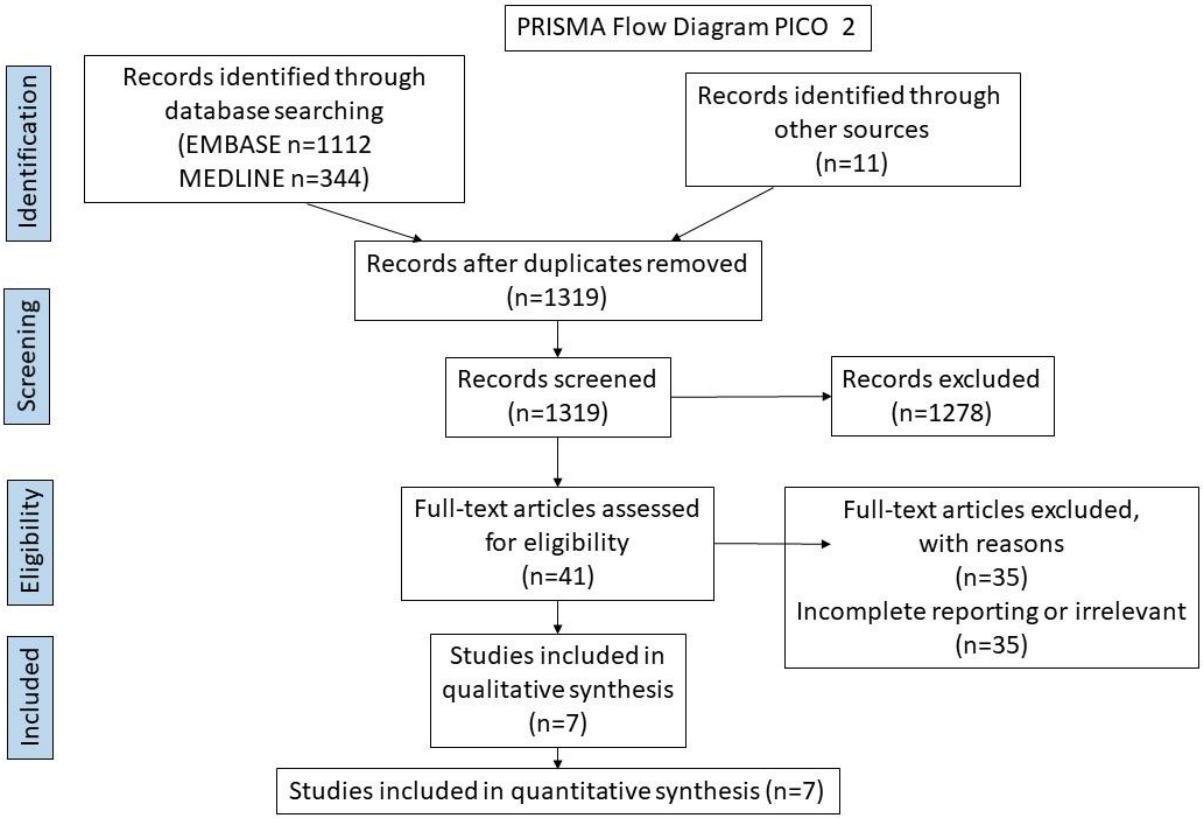
PICO 2



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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 [0.23-0.90]. (RR 0.37 [0.16-0.87], among those	**Methotrexate vs. placebo** Methotrexate was associated with a requirement of lower maintenance dose of systemic glucocorticoids and a decreased weight gain compared to control.

	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 ○ Small ○ Trivial	**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.

○ 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 intervention	**See evidence profiles and section summary** _	

○ 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 ○ Moderate 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.

○ 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 **Pentoxifylline** ○ 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	We found not studies specifically evaluation	The GDG considers that the recommendation is acceptable to key stakeholders.

○ No ○ 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	these drugs in 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	**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

○ 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		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.

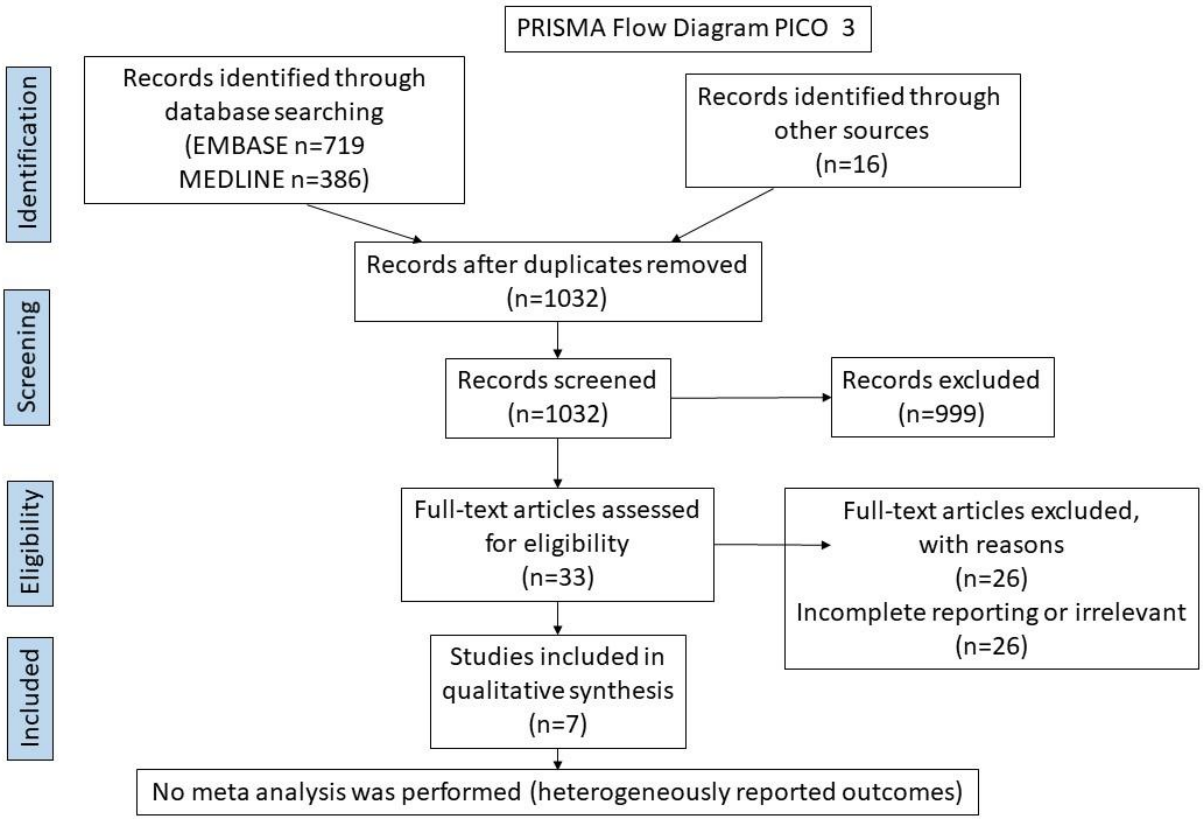
Implementation considerations

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)									

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 --> 2/4 complete	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							remission, 2/4 complete remission with GC + HCQ) I 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. I 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.		

Remission of lupus pernio (follow up: range 18 days to 1659 days; assessed with: Clinical response)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
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.

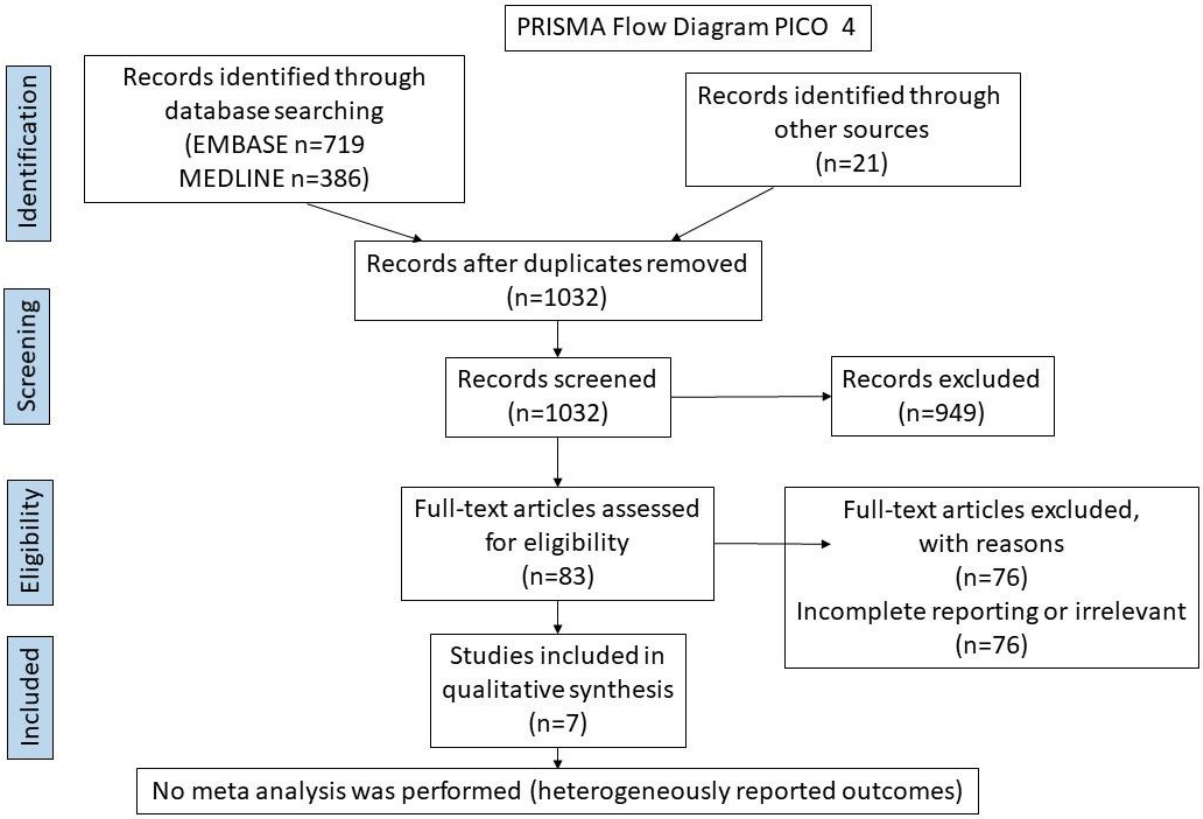
Monitoring and evaluation

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)	Quality	Importance
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	**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

○ Varies ○ 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	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

○ Varies ○ Don't know		
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.

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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 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 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 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 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 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 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.

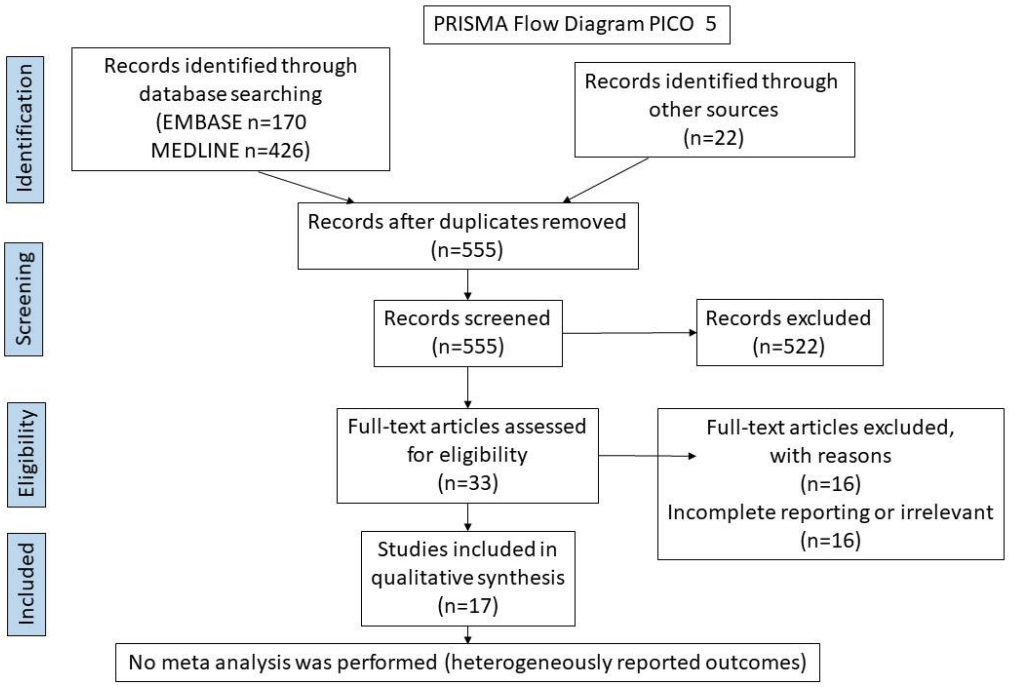
Implementation considerations

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

	JUDGEMENT						
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 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

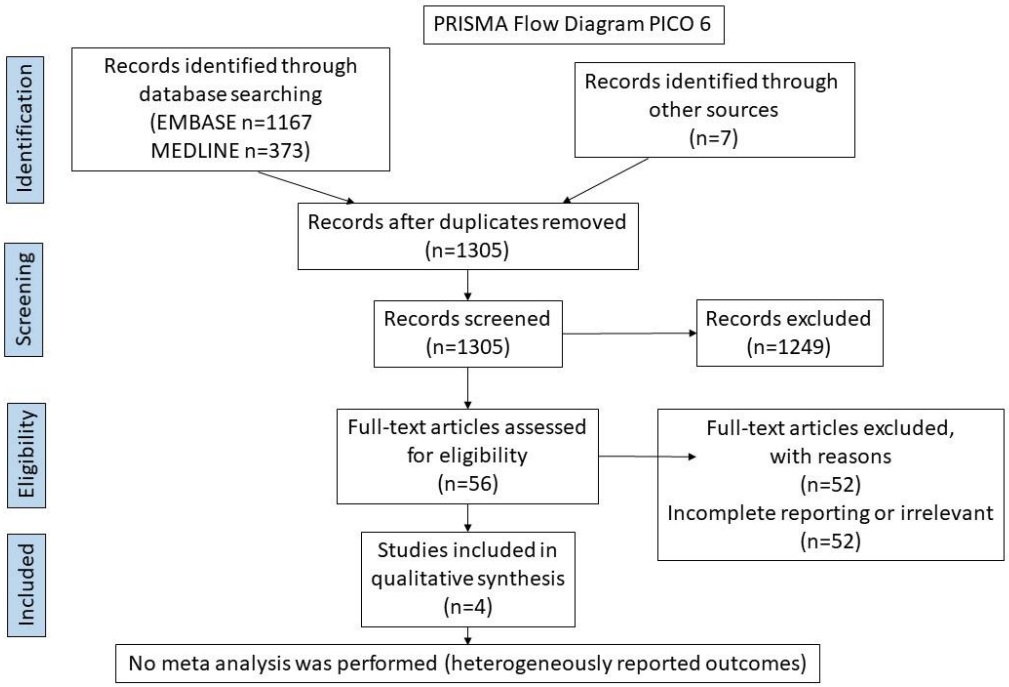
Patients with CS require careful monitoring by cardiologists and sarcoidosis specialists. Side-effects of therapies, including often prolonged glucocorticoid treatment, needs to be assessed regularly. Glucocorticoid-sparing agents may need to be used and the treatment response requires regular assessment,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

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 ○ Don't know	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 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

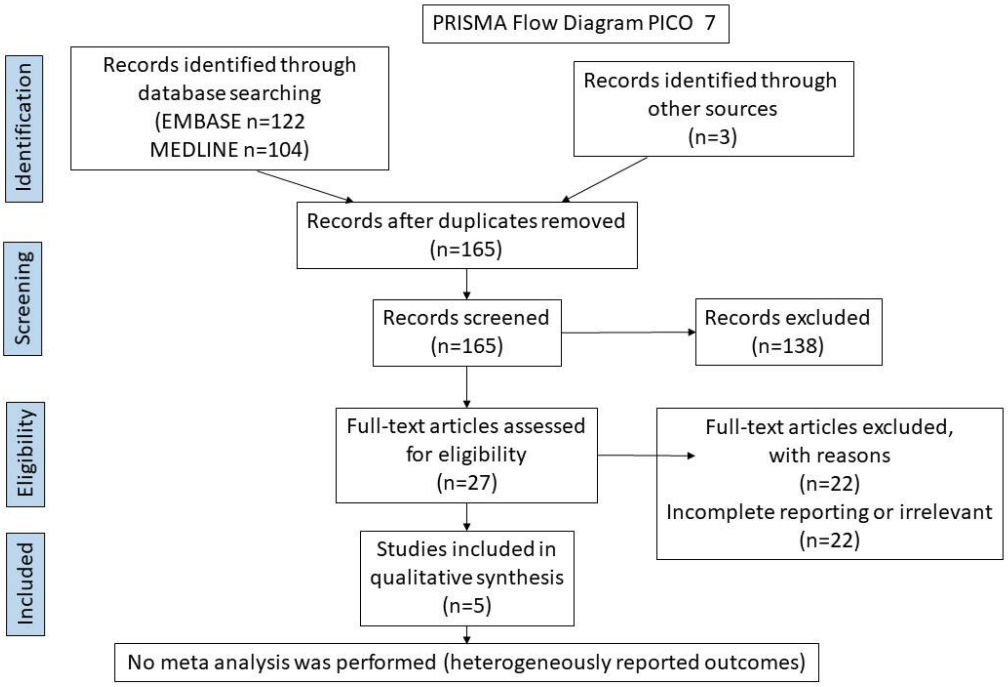
Patients with neurosarcoidosis require regular follow-up, most often with clinical and imaging techniques, such as cerebral magnetic resonance imaging. The use of glucocorticoids requires regular monitoring for expected

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	Seri ous	not serious	not serious	Very seriou s[2]	None	15	15	9 (-0.2-17) for Rx; -5 (-13-1.1) for placeb o	⊕⊕ ◯◯ Low	IMPOR TANT

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)	rando mised trials	Not blin ded	not serious	not	Very seriou s[1]		9	9	40 (31-62) for Int.; -20 (-63-14) for control	⊕◯ ◯◯ VER Y LOW	IMPOR TANT
Borg difference before and after intervention											
1	rando mised trials	Not blin ded	not serious	not	Very seriou s[1]		9	9	-1 (-4-0) for Int.; 0 (-1.5-1) for control	⊕◯ ◯◯ VER Y LOW	IMPOR TANT
MMRC difference before and after intervention											
1	rando mised trials	Not blin ded	not serious	not	Very seriou s[1]		9	9	-1 (-1.5-0) for Int.; 0 (0-0) for control	⊕◯ ◯◯ VER Y LOW	IMPOR TANT
Fatigue severity scale difference before and after intervention											
1	rando mised trials	Not blin ded	not serious	not	Very Seriou s[1]		9	9	-7 (-10-2) for Int.; 1 (0-4) for control	⊕◯ ◯◯	IMPOR TANT

										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 serious 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 serious 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 serious 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 serious 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 serious t	Serious[2]	None	9	9		49.7 (39.3-60.2) for Rx; 21.7 (11.2-32.2) for	⊕⊕◯◯	IMPORTANT

										sham	Low	
Difference in MMRC following intervention												
1	randomised trials	Not serious	not serious	n serio ous 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**	**Dexmethylpheni date 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 serio ous 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 (Interquar		

										tileRange)		
6MWT difference before and after intervention												
1 (61)	randomised trials	Not blinded	not serious	n serious t	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 t	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 t	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 t	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 t	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 t	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 t	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 blin	not seriou	n serious	Very Seriou		9	9		-19 (-25-1) for Int.; -11 (-12-2) for		IMPORTAN

		ded	s	t	s[1]					control		T

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

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**

	JUDGEMENT						
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 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.

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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 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

	JUDGEMENT						
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 recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the	Conditional recommendation for the intervention	Strong recommendation for the intervention

○	○	intervention or the comparison ○	●	○

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.

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.

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

	JUDGEMENT						
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.

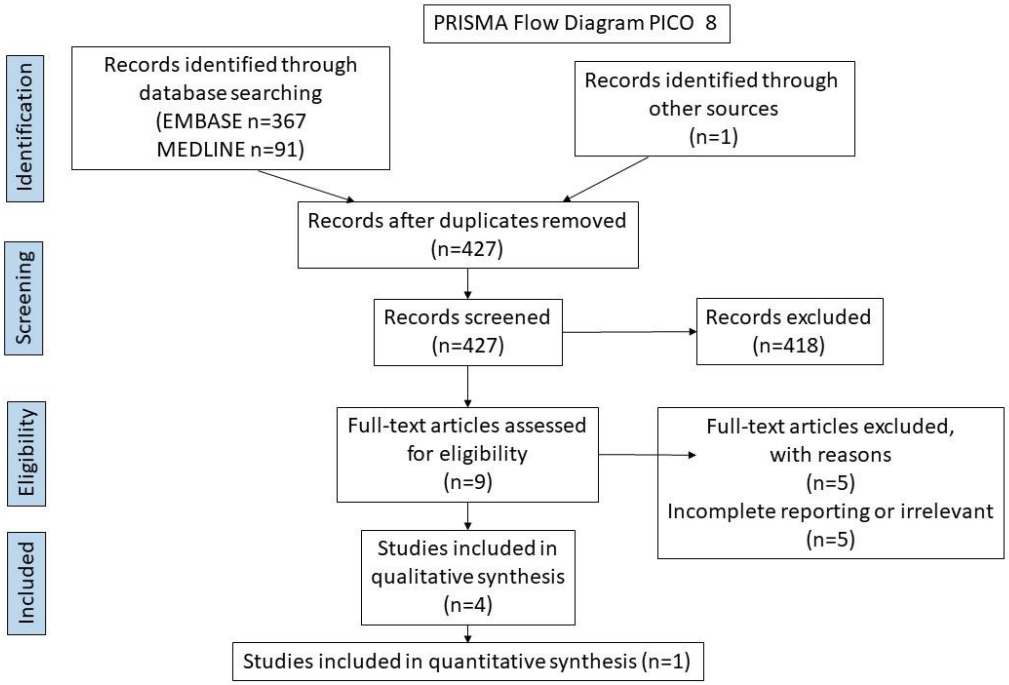
Implementation considerations

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		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	**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

○ Possibly important uncertainty or variability • Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes		practice GDG considers that patients value avoidance of pain. In survey of sarcoidosis patients, overall improvement of quality of 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	**Anti-TNF: No specific studies were identified to answer this question.**	Anti-TNFa: expensive and requires an infusion center

○ Large savings ○ Varies ○ Don't know		
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 ○ 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.
○ 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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