NHS England Evidence Review:

Intravenous infusion of infliximab for the treatment of progressive sarcoidosis (excluding neurosarcoidosis)

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Intravenous infusion of infliximab for the treatment of progressive sarcoidosis (excluding neurosarcoidosis)

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of infliximab, with or without steroids, in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) compared with steroids alone or no treatment.

Progressive disease is defined as aggressive disease that manifests with risk of loss of organ function and/or risk to life and/or significant impairment of quality of life. Studies of patients with any form of chronic sarcoidosis treated with tumour necrosis factor alpha (TNF-α), where there was no indication that their disease was refractory to standard treatment, or that standard treatment is contraindicated were considered for inclusion in this evidence review.

The proposed intervention is for the use of infliximab infusion in patients with progressive sarcoidosis, excluding neurosarcoidosis. Infliximab is a monoclonal antibody that is selectively attaching to TNF-a and blocks its action. It is delivered as an intravenous infusion in addition to the current standard care (corticosteroids and/or at least one DMARD).

In addition, the review scope includes the identification of possible subgroups of people within the included studies who might benefit from infliximab more than others and the criteria used to define progressive sarcoidosis and treatment regimens used for infliximab in the studies.

Infliximab for the treatment of progressive sarcoidosis and for the treatment of refractory sarcoidosis (excluding neurosarcoidosis) are considered in two separate evidence reviews.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of infliximab, with or without steroids, in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) compared with steroids alone or no treatment. The searches for evidence published since January 2012 were conducted on 11 August 2022 and identified 78 references. The titles and abstracts were screened, and 21 full text papers were obtained and assessed for relevance. Given the limited evidence identified on progressive sarcoidosis, it was agreed that case series would also be assessed for relevance.

No papers, comparative or non-comparative, assessing the clinical effectiveness, safety or cost effectiveness of infliximab, with or without steroids, for the treatment of progressive sarcoidosis, (excluding neurosarcoidosis) were identified for this review.

Infliximab for the treatment of refractory sarcoidosis (excluding neurosarcoidosis) is considered in a separate evidence review.

In terms of clinical effectiveness:

- No evidence was identified for the critical outcomes of mortality, health related quality of life (HRQoL) and steroid use reduction.
- No evidence was identified for the important outcomes of sarcoidosis disease activity, organ specific disease activity, radiographic changes and normalisation of inflammatory biomarkers.

In terms of safety:

- No evidence was identified for treatment-emergent adverse events.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients with progressive sarcoidosis that would benefit more from treatment with infliximab.

Definitions of progressive sarcoidosis:

- No studies with a population of patients with progressive sarcoidosis where there is no indication that their disease is refractory to standard treatment, or that standard treatment is contraindicated, were identified for this review.

Treatment regimens for infliximab:

- No evidence was identified for infliximab in patients with progressive sarcoidosis where there is no indication that their disease is refractory to standard treatment, or that standard treatment is contraindicated.

Limitations

No evidence on the clinical effectiveness, safety or cost effectiveness of infliximab, with or without steroids, in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) was identified.

Conclusion

No evidence was identified that allowed any conclusions to be drawn about the clinical effectiveness, safety or cost effectiveness of infliximab, with or without steroids, in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) compared with steroids alone or no treatment. Published studies on the effectiveness of infliximab for progressive sarcoidosis (excluding neurosarcoidosis) are needed.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people with progressive sarcoidosis, excluding neurosarcoidosis, what is the clinical effectiveness of infliximab with or without steroids compared with steroids alone or no treatment?
2. In people with progressive sarcoidosis, excluding neurosarcoidosis, what is the safety of infliximab with or without steroids compared with steroids alone or no treatment?
3. In people with progressive sarcoidosis, excluding neurosarcoidosis, what is the cost effectiveness of infliximab with or without steroids compared with steroids alone or no treatment?
4. From the evidence selected, are there any subgroups of patients that may benefit from infliximab more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define progressive sarcoidosis?
6. From the evidence selected what were the loading dose, loading regime and ongoing schedule/dose used for infliximab?

See Appendix A for the full protocol.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 11 August 2022. PICO details were amended following a telephone conference held on the 15 September 2022.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

As no relevant studies were identified, the appendices for data extraction tables, critical appraisal checklists and GRADE profiles were not completed.

4. Summary of included studies

No papers assessing the clinical effectiveness, safety and cost effectiveness of infliximab, with or without steroids, in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) compared with steroids alone or no treatment were identified for this review.

5. Results

In people with progressive sarcoidosis, excluding neurosarcoidosis, what is the clinical effectiveness and safety of infliximab with or without steroids compared with steroids alone or no treatment?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Mortality **Certainty of evidence:** Not applicable	This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. **No evidence was identified for this outcome.**
HRQoL **Certainty of evidence:** Not applicable	This outcome is important to patients as it provides a holistic evaluation and indication of the patient's general health and perceived wellbeing. **No evidence was identified for this outcome.**
Steroid use reduction **Certainty of evidence:** Not applicable	This outcome is important to those patients receiving steroids because steroid treatment is linked with iatrogenic health problems including osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders. **No evidence was identified for this outcome.**
Important outcomes	
Sarcoidosis disease activity **Certainty of evidence:** Not applicable	This outcome is important to patients because it provides a method of measuring treatment response. **No evidence was identified for this outcome.**
Organ specific disease activity **Certainty of evidence:** Not applicable	These outcomes are important to patients as objective measures of functioning of affected organs. Given the progressive nature of sarcoidosis, disease activity results might not be expected to return to normal following treatment, however, stabilisation may indicate treatment has successfully limited disease progression. **No evidence was identified for this outcome.**
Radiographic changes **Certainty of evidence:** Not applicable	Changes to the appearance of X-rays and scans of affected organs or systems are important to patients as they are used to help determine treatment success and requirement for further treatment. Given the progressive nature of sarcoidosis, imaging results might not be expected to return to normal, however, stabilisation may indicate treatment has successfully limited disease progression and may be associated with improvement in clinical features. **No evidence was identified for this outcome.**
Normalisation of calcium, lymphocytes, ACE and cytokine blood tests **Certainty of evidence:** Not applicable	Assessment of inflammatory biomarkers is important to patients because these blood tests are a quantifiable measure of disease activity and treatment response. Return to normal levels can indicate biochemical remission and may be associated with improvement in clinical features. **No evidence was identified for this outcome.**
Safety	
Serious treatment-emergent adverse events (grade 3, 4 or 5) **Certainty of evidence:** Not applicable	**No evidence was identified for this outcome.**

Outcome	Evidence statement
Treatment-emergent adverse events leading to treatment discontinuation **Certainty of evidence:** Not applicable	**No evidence was identified for this outcome.**
Abbreviations ACE – angiotensin-converting enzyme; HRQoL – health related quality of life	

In people with progressive sarcoidosis, excluding neurosarcoidosis, what is the cost effectiveness of infliximab with or without steroids compared with steroids alone or no treatment?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of patients that may benefit from infliximab more than the wider population of interest?

Outcome	Evidence statement
Subgroups	**No evidence was identified regarding any subgroups of patients with progressive sarcoidosis that would benefit more from treatment with infliximab.**

From the evidence selected, what are the criteria used by the research studies to define progressive sarcoidosis?

Outcome	Evidence statement
Definitions of progressive sarcoidosis	**No studies with a population of patients with progressive sarcoidosis where there is no indication that their disease is refractory to standard treatment, or that standard treatment is contraindicated were identified.**

From the evidence selected what were the loading dose, loading regime and ongoing schedule/dose used for infliximab?

Outcome	Evidence statement
Treatment regimens for infliximab	**No evidence was identified for infliximab in patients with progressive sarcoidosis where there is no indication that their disease is refractory to standard treatment, or that standard treatment is contraindicated.**

6. Discussion

No evidence on the clinical effectiveness, safety or cost effectiveness of infliximab, with or without steroids, in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) compared with steroids alone or no treatment was identified for inclusion in this evidence review.

Searches were conducted on four databases for studies published between January 2012 and August 2022. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, guidelines, case reports and resource utilisation studies were not eligible for inclusion.

7. Conclusion

No evidence was identified that allowed any conclusions to be drawn about the clinical effectiveness, safety or cost effectiveness of infliximab, with or without steroids, in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) compared with steroids alone or no treatment. Well conducted, prospective comparator studies on the clinical effectiveness, safety and cost effectiveness of infliximab, with or without steroids, in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) are needed.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with progressive sarcoidosis, excluding neurosarcoidosis, what is the clinical effectiveness of infliximab with or without steroids compared with steroids alone or no treatment?
2. In people with progressive sarcoidosis, excluding neurosarcoidosis, what is the safety of infliximab with or without steroids compared with steroids alone or no treatment?
3. In people with progressive sarcoidosis, excluding neurosarcoidosis, what is the cost effectiveness of infliximab with or without steroids compared with steroids alone or no treatment?
4. From the evidence selected, are there any subgroups of patients that may benefit from infliximab more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define progressive sarcoidosis?
6. From the evidence selected what were the loading dose, loading regime and ongoing schedule/dose used for infliximab?

P –Population and Indication	People of all ages with progressive sarcoidosis affecting any organ or system except the neurological system where there is no indication that their disease is refractory to standard treatment, or that standard treatment is contraindicated. [Progressive sarcoidosis is defined as aggressive disease that manifests with risk of loss of organ function and/or risk to life and/or significant impairment of quality of life. This applies to any form of chronic sarcoidosis.] [Infliximab is already routinely commissioned for patients with refractory isolated neurosarcoidosis and those with systemic sarcoidosis with refractory, MRI confirmed, neurosarcoidosis. Therefore, populations in studies with single or multiple organ/system sarcoidosis without neurosarcoidosis are of primary interest in this review]
I – Intervention	Intravenous infusion of infliximab (with or without topical or systemic corticosteroids)
C – Comparator(s)	Topical or systemic corticosteroids No treatment
O – Outcomes	<u>Clinical Effectiveness</u> Response to treatment would be expected to be achieved within 6 months of starting treatment. MCIDs are provided where known. <u>*Critical to decision-making:*</u> • Mortality

	This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. [Mortality reported within any timeframe is relevant.] • Health related quality of life (HRQL) *This outcome is important to patients as it provides a holistic evaluation and indication of the patient's general health and perceived wellbeing*. [Disease specific measures include sarcoidosis assessment tool (SAT) for sarcoidosis/skin/fatigue/lung and King's sarcoidosis questionnaire (KSQ) for sarcoidosis/dermatology/lung/general health. Suggested MCIDs are 4 points for the KSQ lung and 8 points for the KSQ GH (Baughman et al, 2021). General measures commonly used are the St George respiratory questionnaire (SGRQ), short form -36 (SF-36) and the fatigue assessment scale (FAS)]. • Steroid use reduction *This outcome is important to those patients receiving steroids because steroid treatment is linked with iatrogenic health problems including osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders.* *Important to decision-making:* • Sarcoidosis disease activity *This outcome is important to patients because it provides a method of measuring treatment response.* [The general tools used to report the outcome are complete response to treatment, partial response to treatment, stable disease and relapse rates] • Organ specific disease activity *These outcomes are important to patients as objective measures of functioning of affected organs. Given the progressive nature of sarcoidosis, disease activity results might not be expected to return to normal following treatment, however, stabilisation may indicate treatment has successfully limited disease progression.* • Lung sarcoidosis disease activity [Pulmonary function measures commonly used to assess this outcome are Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), the fraction between FVC and FEV1 (FVC/FEV1), diffusing capacity of the lungs for carbon monoxide (DLCO), peripheral oxygen saturation (SaO2). The 6 minutes walking test (6-MWT) can also be used] • Cutaneous sarcoidosis disease activity [Disease specific measures include are the cutaneous sarcoidosis activity and morphology instrument (CSAMI) and the sarcoidosis activity and severity instrument (SASI). Suggested MCID for the CSAMI is 5 points (Noe et al., 2020). General measures commonly used include the physician global assessment (PGA) and clinical judgement of improvement with the use of clinical examination or photographs. Suggested MCID for the PGA is 2 points (Baughman et al., 2021)] • Cardiac sarcoidosis disease activity

	[The tools commonly used are the cardiac echocardiography (ECHO), electrocardiography (ECG and 24 hours ECG monitoring), cardiac magnetic resonance imaging (cardiac MRI), the need for implanted pacemakers/defibrillators and clinical judgement of improvement with clinical examination.] • Ophthalmic sarcoidosis disease activity [The tools commonly used are ocular surface disease index scale, retinal thickness, uveitis activity, scleritis activity.] • Renal sarcoidosis disease activity [The tools commonly used are proteinuria (protein levels in the urine) and estimated glomerular filtration rate (eGFR or GFR) as a blood test.] • Hepatic (liver) sarcoidosis disease activity [The tools commonly used are ultrasound scan of the liver to assess for liver disease and blood tests that measure liver enzymes [aspartate aminotransferase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP), Lactate dehydrogenase (LDH) and gamma-glutamyl transferase (GGT)] • Radiographic changes Changes to the appearance of X-rays and scans of affected organs or systems are important to patients as they are used to help determine treatment success and requirement for further treatment. Given the progressive nature of sarcoidosis, imaging results might not be expected to return to normal, however, stabilisation may indicate treatment has successfully limited disease progression *and may be associated with improvement in clinical features*. [X-rays, computerised tomography scans (CT) and positron emission tomography (PET) can used to determine treatment changes.] • Normalisation of calcium, lymphocytes, angiotensin-converting enzyme (ACE) and cytokine blood tests *Assessment of inflammatory biomarkers is important to patients because these blood tests are a quantifiable measure of disease activity and treatment response. Return to normal levels can indicate biochemical remission and may be associated with improvement in clinical features.* <u>Safety</u> • Presence of serious treatment-emergent adverse events (grade 3, 4 or 5) including but not limited to tuberculosis, invasive fungal infections, Hepatitis B reactivation, hepatobiliary events, neurological events, malignancies. • Treatment-emergent adverse events leading to treatment discontinuation. <u>Cost effectiveness</u>
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies.

	If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2012-2022
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines
Study design	Case reports, resource utilisation studies

PICO details were amended following a telephone conference with NHS England held on 15 September 2022.

Appendix B Search strategy

Medline, Embase, the Cochrane Library and TRIP were searched, limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, guidelines, case reports and resource utilisation studies were excluded.

One search was conducted for infliximab for the treatment of progressive sarcoidosis and refractory sarcoidosis (excluding neurosarcoidosis).

Search dates: 1946 to 11 August 2022

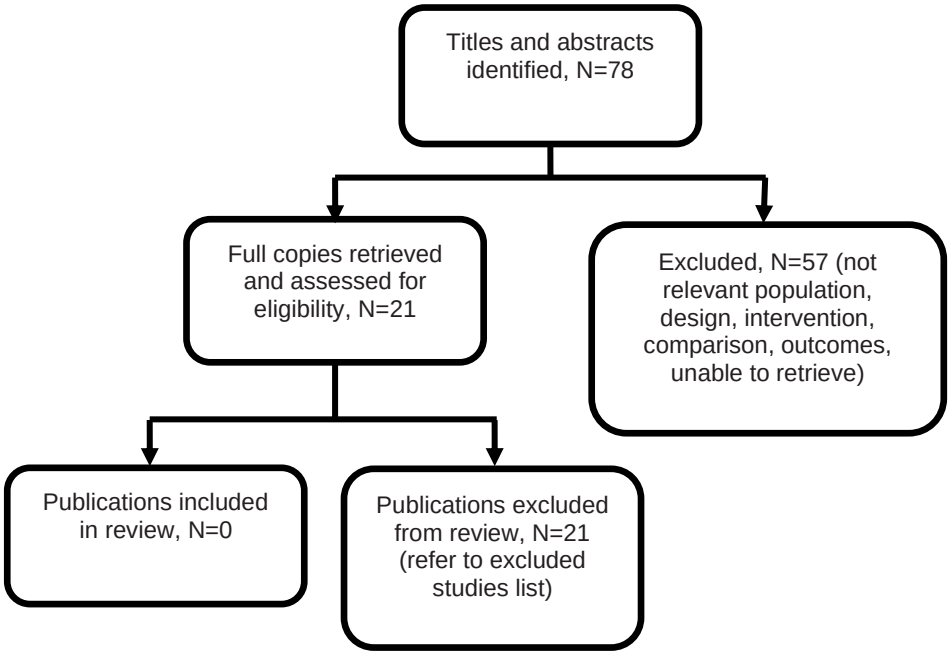
Medline search strategy:

1	sarcoidosis/ or sarcoidosis, pulmonary/
2	sarcoidosis.ti,ab,kf.
3	1 or 2
4	(neurosarcoidosis not sarcoidosis).ti.
5	3 not 4
6	Infliximab/
7	(infliximab or avsola or inflectra or remicade or renflexis).ti,ab,kf.
8	Tumor Necrosis Factor Inhibitors/tu [Therapeutic Use]
9	(anti-tnf or anti-tumo?r necrosis factor or tumo?r necrosis factor inhibitor?).ti.
10	6 or 7 or 8 or 9
11	5 and 10
12	exp animals/ not humans/
13	11 not 12
14	limit 13 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
15	(comment or editorial or letter or news or "review").pt.
16	13 not 15
17	14 or 16
18	limit 17 to (english language and yr="2006 -Current")

Appendix C Evidence selection

The combined literature searches for infliximab in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) identified 78 references. These were screened using their titles and abstracts and 21 references were obtained in full text and assessed for relevance. Of these, 0 references are included in this evidence review. The 21 references excluded are listed in Appendix D. Studies relating to infliximab for the treatment of progressive sarcoidosis and refractory sarcoidosis (excluding neurosarcoidosis) are considered in separate evidence reviews.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Adler BL, Wang JC, Bui T, Schilperoort HM, Armstrong AW. 2019. Anti-tumor necrosis factor agents in sarcoidosis: A systematic review of efficacy and safety. Seminars in Arthritis and Rheumatism June;48(6), pp.1093-1104.	Excluded This systematic review includes 65 studies of which 22 studies assessed infliximab for different types of refractory sarcoidosis, including out of scope patients with neurosarcoidosis. The 22 individual studies were assessed against the PICO criteria; 12 studies were ineligible for inclusion as they were published pre-2012; two studies were excluded because they had an ineligible study design; eight studies were excluded as the study populations did not meet the definition of progressive sarcoidosis. Studies for refractory sarcoidosis are out of scope of this review of infliximab for progressive sarcoidosis, but were considered for inclusion in the review of infliximab for refractory sarcoidosis.

Reference	Paper selection - decision and rationale if excluded
Sakkat, A. et al., 2022. Infliximab therapy in refractory sarcoidosis: A multicenter real-world analysis. Respiratory Research, 23(1).	Excluded The population meets the criteria for refractory sarcoidosis. Not within the scope of this review on patients with progressive sarcoidosis with no indication that their disease is refractory to standard treatment, or that standard treatment is contraindicated.
Full evidence summary | Refractory extrapulmonary sarcoidosis: infliximab | Advice | NICE. [online] Available at: https://www.nice.org.uk/advice/es4/chapter/Full evidence-summary#relevance-to-nice-guidance-programmes.	Excluded The NICE evidence summary includes studies of populations that meet the criteria for refractory sarcoidosis. Not within the scope of this review on patients with progressive sarcoidosis with no indication that their disease is refractory to standard treatment, or that standard treatment is contraindicated.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Adler BL, Wang CJ, Bui TL, Schilperoort HM, Armstrong AW. Anti-tumor necrosis factor agents in sarcoidosis: A systematic review of efficacy and safety. Semin Arthritis Rheum. 2019;48(6):1093-104.	This systematic review included 65 studies of which only 22 studies assessed infliximab for different types of refractory sarcoidosis, including out of scope patients with neurosarcoidosis. Studies for refractory sarcoidosis are out of scope of this review of infliximab for progressive sarcoidosis but were considered for inclusion in the review of infliximab for refractory sarcoidosis. References were checked for populations meeting PICO criteria; 12 were out of scope as they were published pre-2012; 2 studies were not relevant because they had an ineligible study design; the remaining 8 studies were excluded from this review as the populations had refractory disease.
Adler B, Wang C, Bui T, Schilperoort H, Armstrong AW. Efficacy and safety of tumor necrosis factor inhibitors in cutaneous sarcoidosis: A systematic review. Journal of Investigative Dermatology. 2018;138(5 Supplement 1): S74.	The systematic review did not meet PICO criteria for publication type (i.e. conference abstract only).
Baker MC, Sheth K, Witteles R, Genovese MC, Shoor S, Simard JF. TNF-alpha inhibition for the treatment of cardiac sarcoidosis. Seminars in Arthritis and Rheumatism. 2020;50(3):546-52.	The study does not meet PICO criteria because the 10 patients who received infliximab were already receiving methotrexate (i.e. refractory sarcoidosis).
Bakker ALM, Mathijssen H, Azzahhafi J, Swaans MJ, Veltkamp M, Keijsers RGM, et al. Effectiveness and safety of infliximab in cardiac Sarcoidosis. Int J Cardiol. 2021; 330:179-85.	This retrospective, single centre cohort study did not meet PICO criteria because the majority of patients were refractory to first- and second-line immunosuppressive therapy. 19 of 22 patients had refractory cardiac sarcoidosis with persistent inflammation on FDG-PET/CT and the remaining three patients suffered from severe side effects from first or second-line agents.
Baughman RP, Lower EE, Ingledue R, Kaufman AH. Management of ocular sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2012;29(1):26-33.	The study population does not meet PICO criteria because it includes patients with refractory disease; of 365 patients receiving methotrexate, 25 received additional anti-TNF agents (n=19 received infliximab and n=6 received adalimumab) due to developing refractory disease.
Baughman RP, Lower EE. Frequency of acute worsening events in fibrotic pulmonary sarcoidosis patients. Respir Med. 2013;107(12):2009-13.	The study authors do not specify which anti-TNF treatment patients received and outcomes are only reported for patients receiving versus patients not receiving anti-TNF antibodies.
Baughman RP, Judson MA, Lower EE, Drent M, Costabel U, Flavin S, et al. Infliximab for chronic cutaneous sarcoidosis: a subset analysis from a double-blind randomized clinical trial. Sarcoidosis Vasc Diffuse Lung Dis. 2016;32(4):289-95.	This study does not meet PICO criteria because the study population (n=17 patients with chronic cutaneous sarcoidosis) had previously received treatments in addition to steroids (i.e. refractory sarcoidosis).
Baughman RP, Cremers JP, Harmon M, Lower EE, Drent M. Methotrexate in sarcoidosis: hematologic and hepatic toxicity encountered in a large cohort over a six year period. Sarcoidosis Vasc Diffuse Lung Dis. 2020;37(3): e2020001.	The study population does not meet PICO criteria because the 607 patients included in the study were receiving methotrexate; of these 607 patients, 44 patients also received infliximab (i.e. refractory sarcoidosis).
Cacciatore C, Belnou P, Thietart S, Desthieux C, Versini M, Abisror N, et al. Acute and Chronic Sarcoid	The case report does not meet PICO criteria because the population includes 19/39 patients with acute

Study reference	Reason for exclusion
Arthropathies: Characteristics and Treatments From a Retrospective Nationwide French Study. Front Med (Lausanne). 2020; 7:565420.	sarcoidosis. Of the 20 patients with chronic sarcoidosis, five received third-line therapy with TNF inhibitors, but there was no mention of which TNF inhibitors were used.
Galli F, Lanzolla T, Pietrangeli V, Malviya G, Ricci A, Bruno P, et al. In vivo evaluation of TNF-alpha in the lungs of patients affected by sarcoidosis. Biomed Res Int. 2015; 2015:401341.	This study was excluded as although half of the study population (n=10) met the criteria for progressive sarcoidosis, none of the outcomes reported were in scope. Outcomes were out of scope because data assessed which organs were involved in disease activity and evaluated the presence/uptake of anti-TNF-α drugs in sarcoid lesions at 6 and 24 hours to act as a marker for predicting the efficacy of treatment with infliximab and determine which patients are most suitable for this type of treatment (i.e. the study did not report improvements in symptoms/success of treatments).
Gallegos C, Oikonomou EK, Grimshaw A, Gulati M, Young BD, Miller EJ. Non-steroidal treatment of cardiac sarcoidosis: A systematic review. Int J Cardiol Heart Vasc. 2021; 34:100782.	The systematic review did not meet PICO criteria because only 13/23 studies assessed infliximab for cardiac sarcoidosis. The 13 references were assessed against the PICO criteria; nine were excluded due to the study design (i.e. conference abstracts); four studies were excluded due to the study populations having refractory sarcoidosis.
Gilotra NA, Wand AL, Pillarisetty A, Devraj M, Pavlovic N, Ahmed S, et al. Clinical and Imaging Response to Tumor Necrosis Factor Alpha Inhibitors in Treatment of Cardiac Sarcoidosis: A Multicenter Experience. Journal of Cardiac Failure. 2021;27(1):83-91.	The study population and outcomes reported do not meet PICO criteria. The population includes patients with cardiac sarcoidosis and extracardiac sarcoidosis who were treated with TNF alpha inhibitors (infliximab or adalimumab); all 38 patients had at some point been treated with prednisone and 36 patients with a steroid-sparing agent (SSA) (i.e. refractory disease).
Hostettler KE, Studler U, Tamm M, Brutsche MH. Long-term treatment with infliximab in patients with sarcoidosis. Respiration. 2012;83(3):218-24.	The study population in this non-comparative study does not meet PICO criteria because it includes patients with refractory sarcoidosis (28 patients had steroid-resistant disease or were refractory to steroid-sparing agents or had developed severe side effects under these treatments).
Judson MA, Baughman RP, Costabel U, Mack M, Barnathan ES. The potential additional benefit of infliximab in patients with chronic pulmonary sarcoidosis already receiving corticosteroids: a retrospective analysis from a randomized clinical trial. Respir Med. 2014;108(1):189-94.	The study population was out of scope because the 122 patients had chronic, symptomatic pulmonary sarcoidosis despite previous treatment; all patients received ≥10 mg daily of prednisone or its equivalent and/or methotrexate, azathioprine, or hydroxychloroquine for ≥3 months prior to randomisation (i.e. refractory sarcoidosis).
Kullberg S, Rivera NV, Grunewald J, Eklund A. Effects of infliximab on lung and circulating natural killer cells, CD56+ T cells and B cells in sarcoidosis. BMJ Open Respir Res. 2021;8(1):07.	The study population does not meet the population criteria in the PICO; 15 of 16 patients with deteriorating pulmonary sarcoidosis had received previous treatment with corticosteroids and/or methotrexate i.e. refractory sarcoidosis. The authors stated that "All patients except number 2 had a history of both prednisone and methotrexate treatment. Patient number 2 was regarded as having a very active disease despite high-dose prednisone, and the clinical decision was that it was better for the patient to start with infliximab than methotrexate". Therefore, only one patient who had not previously received prednisone and methotrexate met PICO criteria; outcome data were not reported separately for this patient.

Study reference	Reason for exclusion
Maneiro JR, Salgado E, Gomez-Reino JJ, Carmona L, Group BS. Efficacy and safety of TNF antagonists in sarcoidosis: data from the Spanish registry of biologics BIOBADASER and a systematic review. Semin Arthritis Rheum. 2012;42(1):89-103.	This systematic review was excluded from this review as it included studies published pre-2012 as well as studies of patients with refractory sarcoidosis. The case series (BIOBADASER) did not meet PICO criteria because it included refractory patients; of 8 patients, 62.5% had received prior treatment with steroids and 75.5% had received previous treatment with DMARDs (methotrexate or azathioprine).
Shah P, Bechman K, Galloway J. The evidence for biologic immunotherapy in Sarcoidosis: A systematic review. Australasian Medical Journal. 2017;10(9):829-37.	The systematic review did not meet PICO criteria because it included in-scope and out of scope studies (n=5 RCTs); 2 RCTs assessed infliximab for pulmonary sarcoidosis and were potentially in scope. Both were assessed individually for inclusion against the PICO criteria (Appendix A) but did not meet the inclusion criteria as they were published pre-2012 (Baughman 2006; Rossman 2006).
Stievenart J, Le Guenno G, Ruivard M, Rieu V, Andre M, Grobost V. Case Report: TNFalpha Antagonists Are an Effective Therapy in Cardiac Sarcoidosis. Front. 2021; 8:676407.	The case report does not meet PICO criteria because the population included four patients with cardiac sarcoidosis treated with infliximab or adalimumab after the first or second cardiac sarcoidosis relapse when taking corticosteroid therapy and immunosuppressive therapy (i.e. refractory sarcoidosis).
Verwoerd A, Hijdra D, Vorselaars AD, Crommelin HA, van Moorsel CH, Grutters JC, et al. Infliximab therapy balances regulatory T cells, tumour necrosis factor receptor 2 (TNFR2) expression and soluble TNFR2 in sarcoidosis. Clin Exp Immunol. 2016;185(2):263-70.	The population was out of scope because patients with severe sarcoidosis were reported to be unresponsive to first- and second-line treatment (including treatments with corticosteroids, methotrexate, azathioprine, leflunomide, plaquenil, anti-TNF treatment) or had experienced severe side-effects from these agents, e.g., worsening diabetes, psychological deterioration or liver function disorders (i.e. refractory sarcoidosis).
Wanat KA, Rosenbach M. Case series demonstrating improvement in chronic cutaneous sarcoidosis following treatment with TNF inhibitors. Archives of Dermatology. 2012;148(9):1097-100.	The commentary was excluded as it was a case series of patients with chronic, persistent, refractory cutaneous lesions that failed to respond to alternative medications.
Xue L, van Bilsen K, Schreurs MWJ, van Velthoven MEJ, Missotten TO, Thiadens AAHJ, et al. Are Patients at Risk for Recurrent Disease Activity After Switching From Remicade to Remsima? An Observational Study. Front Med (Lausanne). 2020; 7:418.	The study population does not meet PICO criteria because it includes patients with out-of-scope inflammatory diseases (Behçet's Disease, non-infectious uveitis, and other diagnoses). Patients had received off-label infliximab treatment because of previously refractory disease and/or unacceptable side effects to standard immunosuppressive agents. In addition, the study inclusion criteria stated that patients must have stable disease (i.e. not progressive disease).

Appendix E Evidence table

No papers assessing the clinical effectiveness, safety or cost effectiveness of infliximab, with or without steroids, in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) were identified for this review.

Appendix F Quality appraisal checklists

No checklists were used in this review.

Appendix G GRADE profiles

No papers assessing the clinical effectiveness, safety or cost effectiveness of infliximab, with or without steroids, in the treatment of progressive sarcoidosis (excluding neurosarcoidosis) were identified for this review.

Glossary

Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into four components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Systematic review	A review that summarises the evidence on a clearly formulated review question according to a predefined protocol, using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, analyse, collate and report their findings. It may or may not use statistical techniques, such as meta-analysis.

References

Included studies

No studies were identified for inclusion.

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