NHS England Evidence Review:

Intravenous infusion of infliximab for refractory sarcoidosis (excluding neurosarcoidosis)

NHS England URN: 2204a

NHS England Evidence Review

Intravenous infusion of infliximab for refractory sarcoidosis (excluding neurosarcoidosis)

Completed: November 2022

Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of infliximab (IFX) and current standard care compared with current standard care for the treatment of refractory sarcoidosis, excluding neurosarcoidosis,

Refractory sarcoidosis is defined as sarcoid disease that has failed to respond to corticosteroids and/or at least one Disease Modifying Anti-Rheumatic Drug (DMARD) or where there is contra-indication or intolerance in treatment with those agents (current standard care).

Infliximab (IFX) is a monoclonal antibody that selectively attaches to tumour necrosis factor-alpha (TNF-α) and blocks its action. TNF-α plays an essential role in the pathophysiology of sarcoidosis. IFX is given by intravenous infusion in addition to the current standard care (corticosteroids and/or at least one DMARD).

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from infliximab more than others, the criteria used by the included studies to define refractory sarcoidosis and the dosage (loading dose, loading regime and ongoing schedule/dose used) of infliximab used.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of infliximab (IFX) and current standard care compared with current standard care for the treatment of patients with refractory sarcoidosis, excluding neurosarcoidosis. Refractory sarcoidosis is defined in the description of the population in the Appendix A PICO document. The searches for evidence published since January 2006 were conducted on 11 August 2022 and identified 289 references. The titles and abstracts were screened, and 40 full-text papers were obtained and assessed for relevance.

Seven papers were identified for inclusion: one small randomised controlled trial (RCT) with 19 participants (13 treated with IFX and 6 placebo), one prospective case series and five retrospective case series, which included between 30 and 56 people. Studies ranged in length from the six-week RCT to up to 12 months. The majority of included studies used a dose of 5mg/kg intravenous (IV) IFX, with treatment duration ranging from two weeks to 12 months. Studies took place in the USA, The Netherlands, France, Canada and the UK.

In terms of clinical effectiveness:

- **Mortality (critical).** One RCT provided very low certainty evidence that the mortality rate in people treated with IFX for refractory sarcoidosis is 7.7% at six weeks (based on one death in a very small RCT); none of the six patients being treated with placebo (PB) died during this period. No between-group comparison or statistical significance was reported. Six case series provided very low certainty evidence that the mortality rate for patients being treated with IFX for refractory sarcoidosis is 0% to 2% at up to six months and 0% to 3% at 12 months.
- **Health-related quality of life (HRQL) (critical).** One RCT provided low certainty evidence of limited improvement from baseline HRQL at six weeks for people with pulmonary sarcoidosis treated with IFX (statistical significance not reported), with no change from baseline in the PB group. No between-group comparison was reported. Two case series provided very low certainty evidence of statistically significant improvements from baseline fatigue severity and physical functioning at 18 weeks to six months for people with mixed sarcoidosis. No disease-specific HRQL measures were reported.
- **Steroid use reduction (critical).** Although one case series provided very low certainty evidence of no reduction in steroid use at 18 weeks, statistically significant reductions in steroid dose compared to baseline after six months (3 case series) and 12 months (4 case series) of treatment with IFX were reported, with dose reductions in the region of 9 to 15mg per day.
- **Sarcoid disease activity (important).** Four case series provided very low certainty evidence that the majority of people (67% to 96%) treated with IFX for refractory sarcoidosis were classified as having at least partial response at six to 12 months, although definitions of response varied between studies and reduction in sarcoid disease activity was not maintained in 35 to 64% of responders.
- **Organ-specific disease activity (important).** One RCT provided low certainty evidence of improvements in vital capacity (VC) from baseline to six weeks but did not report statistical significance or a statistical comparison with the placebo arm. One case series provided very low certainty evidence of statistically significant improvements in percentage predicted forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and diffusing capacity of the lungs for carbon monoxide (DLCO) at 18 weeks. One case series reported statistically significant improvements from baseline to

six months for FVC, FEV1 and DLCO for the subgroup of people with pulmonary indication, and also reported improved 6MWD at six months (statistical significance not reported) for this subgroup. One case series provided very low certainty evidence that changes in pulmonary function did not appear to be significant at 12 months, although 78.6% were considered to have had treatment success at that time, (defined as an increase in absolute FVC or FEV1 by >10% or no change in FVC or FEV1 (± 10% from baseline). The clinical significance of any changes from baseline was not reported.

In terms of cardiac function, very low certainty evidence from two case series suggests that, compared to baseline, there were no statistically significant changes in left ventricular ejection fraction (LVEF), ejection fraction (EF) and implantable cardioverter defibrillator (ICD) therapy use at six or 12 months.

Very low certainty evidence from one case series reported that 24% of people treated with IFX for refractory cutaneous sarcoidosis responded at three months, rising to 46% at six months. At 12 months, results from two case series reported that the proportion of responders to IFX was between 79% and 92%.

- **Radiographic changes (important).** One RCT provided low certainty evidence of radiologic improvement at six weeks in people with refractory pulmonary sarcoidosis but did not report statistical significance or a statistical comparison with the placebo group. There was very low certainty evidence of significant improvements from baseline at 18 weeks (one case series) and six months (one case series) in people with refractory mixed sarcoidosis. Another case series reported improvements from baseline to six and 12 months in people with refractory cardiac sarcoidosis but did not report statistical significance.
- **Normalisation of calcium, lymphocytes, angiotensin-converting enzyme (ACE) and cytokine blood tests (important).** None of the studies provided evidence for calcium, lymphocytes and cytokine blood tests. Two case series provided very low certainty evidence of statistically significant reductions in ACE and serum soluble interleukin-2 receptor (sIL-2R).

In terms of safety:

- There was low certainty evidence of an adverse event (AE) rate of approximately 15% (2/13 patients in one RCT) at six weeks, and very low certainty evidence that approximately 2% to 5% of people may experience an SAE at 18 weeks to six months (two case series). Very low certainty evidence from one case series suggests that around 15% of people on IFX may experience a grade 3 or 4 infection requiring hospitalisation at 12 months.
- One RCT provided low certainty evidence of a 15% discontinuation rate at six weeks (with a similar rate in the PB arm), and six case series provided very low certainty evidence of a wide range of discontinuation rates at 18 weeks to 12 months, ranging from approximately 2% to 24%.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- One case series provided very low certainty evidence that there may be little difference in overall cutaneous response rate (OCRR) between people with skin-only indication for

IFX and those with visceral involvement. People with skin-only indication may have more need for systemic steroids but may have fewer infections than those with visceral involvement.

- One case series reported results following treatment with IFX for a subgroup of people with pulmonary indication, and found that serum ACE levels were lower in this subgroup than in people with extrapulmonary indication.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

The only RCT identified was small, underpowered and only treated patients for two weeks, with follow-up at six weeks. The majority of evidence comes from non-comparative case series, with serious limitations in terms of indirectness, and the possibility of selection bias due to the nature of retrospective database studies. Four case series included between 14% and 33% of people with central nervous system involvement or small fibre neuropathy, and outcome data were generally not available separately for patients within scope for this review. In two case series, 13% and 21% of patients had adalimumab or etanercept rather than IFX, and outcome data were not available separately for those who had IFX. A large proportion of the included patients had mixed sarcoidosis, and even those studies that focussed on particular organs (e.g. cardiac or skin) contained substantial proportions of people with multiple organ involvement. It is not clear whether or not this may affect response to IFX treatment or patient outcomes. Duration of sarcoidosis/severity of disease varied or was not reported in a way that allowed comparisons across studies. The reporting of adverse events was not clear in many of the studies, making it difficult to distinguish treatment-emergent serious adverse events from other adverse events. The retrospective records-based nature of the majority of the studies means that there may be some ambiguity in the reporting of these, particularly where timescales of follow-up are unclear.

Conclusion

The evidence base for this review was of very low certainty due to its broadly non-comparative nature. It is therefore not possible to reach any conclusions about the clinical effectiveness and safety of IFX compared to standard care alone for the treatment of people with refractory sarcoidosis, excluding neurosarcoidosis.

Longer-term published studies would be informative for mortality rates, but none were available for inclusion in this evidence review. Although none of the case series reported if treatment effects reached clinically significant proportions or offered significant benefit to patients, there was very low certainty evidence of statistically significant changes from baseline for reduced steroid dose, improved fatigue and physical function, and the majority of patients had at least a partial response to treatment with IFX.

No evidence was available for the cost effectiveness of IFX for sarcoidosis.

3. Methodology

Review questions

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

1. In people with refractory sarcoidosis, excluding neurosarcoidosis, what is the clinical effectiveness of infliximab combined with current standard care compared with current standard care alone?

2. In people with refractory sarcoidosis, excluding neurosarcoidosis, what is the safety of infliximab combined with current standard care compared with current standard care alone?

3. In people with refractory sarcoidosis, excluding neurosarcoidosis, what is the cost-effectiveness of infliximab combined with current standard care compared with current standard care alone?

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 refractory 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 PICO document.

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.

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 document. Full text of potentially relevant studies 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.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Seven papers were identified for inclusion (Gilotra et al 2021, Harper et al 2019, Heidelberger et al 2017, Rossman et al 2006, Sakkat et al 2022, van Rijswijk et al 2013, Vorselaars et al 2015). Table 1 provides a summary of these included studies and full details are given in Appendix E.

One paper reported an RCT (Rossman et al 2006) and six are included in this review as case series as they are not comparative (Gilotra et al 2021, Harper et al 2019, Heidelberger et al 2017, Sakkat et al 2022, van Rijswijk et al 2013, Vorselaars et al 2015).

No cost effectiveness studies suitable for inclusion in this evidence review were identified.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Gilotra et al 2021 Retrospective case series USA (2 institutions' Cardiac Sarcoidosis Registries)	• 38 patients with cardiac sarcoidosis • 30 treated with IFX, 8 with adalimumab • No subgroups reported	**Intervention** IFX IV infusion 5mg/kg: 21/30 (70%) Prednisone: n = 33/38 (87%) **Comparison** None	**Critical outcomes** Reported at 12 months • Mortality • Steroid use reduction **Important outcomes** Reported at baseline, 6 months and 12 months • Organ-specific disease activity: cardiac function (LVEF) • Radiographic changes (SUVmax) Reported at any time during study • SAE (during treatment) • AE leading to discontinuation
Harper et al 2019 Retrospective case series Cleveland, USA	• 36 patients with cardiac sarcoidosis, some with additional involvement (heart 36 (100%); lung 26 (72%); neurologic 12 (33%); skin 7 (19%); other 10 (28%)) • No subgroups reported	**Intervention** 5 mg/kg IFX every 4 to 6 weeks with titration up to 10 mg/kg for lack of response and lengthening of dosing interval to every 8 weeks if the patient exhibited stability. 35 patients completed at least 6 months and 29 completed at least 1 year of IFX. Steroid use at IFX initiation: 32 (89%) **Comparison** None	**Critical outcomes** • Mortality, reported at 12 months • Steroid use reduction, mean dose reported at baseline, 6 months, 12 months **Important outcomes** • Sarcoid disease activity: responder/non-responder/stable, reported at 12 months • Organ-specific disease activity: cardiac function, reported at baseline, 6 months, 12 months (EF; ICD therapy) Reported at any time up to 12 months • SAE • AE leading to discontinuation
Heidelberger et al 2017	• 46 patients with cutaneous sarcoidosis • Subgroups: skin-only indication (n=21) vs	**Intervention** IFX: 40 (87%)	**Critical outcomes** • Mortality (reported at up to 12 months)

Study	Population	Intervention and comparison	Outcomes reported
Retrospective case series France (review of multicentre database)	visceral involvement (n=25).	Adalimumab: 5 (11%) Etanercept: 1 (2%) Concomitant prednisone (n=28), methotrexate (n=26) or other IS (n=6) **Comparison** None	• Steroid use reduction (mean dose at baseline and last follow-up (up to 12 months) **Important outcomes** • Sarcoid disease activity (responders) at up to 12 months • Organ-specific disease activity: OCRR, reported at 3, 6, 12 months • ePOST at baseline and last follow-up (up to 12 months) • SAE (not reported separately from AE) at any time point • AE leading to discontinuation, reported at any time point
Rossman et al 2006 Multicentre RCT USA	• 19 patients with pulmonary sarcoidosis • IFX n=13; PB n=6 • No subgroups reported	**Intervention** IFX 5mg/kg at weeks 0 and 2 Concomitant CCS: 9/13 (69.2%) **Comparison** PB at weeks 0 and 2 Concomitant CCS: 4/6 (66.7%)	**Critical outcomes** • Mortality, reported at 6 weeks • HRQL: SF36, reported at baseline and 6 weeks **Important outcomes** • Organ-specific disease activity: pulmonary function (vital capacity, dyspnoea index), reported at baseline and 6 weeks • Radiographic changes: radiologic improvement, reported at 6 weeks • AE, reported at any time up to 6 weeks • AE leading to discontinuation, reported at any time up to 6 weeks
Sakkat et al 2022 Retrospective case series Canada and UK (databases from 3 tertiary referral centres)	• 33 patients with mixed sarcoidosis: lungs n=14; skin: n=12; upper airway: n=7; CNS: n=6; other: n=4 • No subgroups reported	**Intervention** IFX: 3–5 mg/kg dose at 0, 2 and 6 weeks, then every 4–8 weeks, individualised duration **Concomitant therapy** • Corticosteroid alone: n=5 • 2nd line immunosuppressive alone: n=9 • Corticosteroid + 2nd line immunosuppressive: n=19 **Comparison** None	**Critical outcomes** Reported at end of follow-up (varied, but 12 months for most patients) • Mortality • Steroid use reduction, reported at baseline and end of follow-up **Important outcomes** • Sarcoid disease activity (relapse), reported with median time to relapse • Organ-specific disease activity: pulmonary function (FEV1, FVC) • Organ-specific disease activity, treatment success, with organ-specific definition. Presented for: pulmonary function; cutaneous; upper airway; peripheral lymph nodes; gastrointestinal; uveitis; arthritis.

Study	Population	Intervention and comparison	Outcomes reported
			• SAE • AE leading to discontinuation
Van Rijswijk et al 2013 Retrospective case series Nieuwegein, The Netherlands	• 45 patients with mixed sarcoidosis: 23 pulmonary, 23 extrapulmonary (uveitis n=4, cardiac n=2, neurosarcoidosis and SFN n=9, extreme fatigue n=7) • No subgroups reported	**Intervention** IFX (IV) 5 mg/kg at weeks 0, 2, 6, 10, 14 and 18. Concomitant medication • Methotrexate 16 (35.6%) • Prednisone 16 (35.6%) • Prednisone and methotrexate 8 (17.8%) • Plaquenil 1 (2.2%) • None 3 (6.7%) • Unknown 1 (2.2%) **Comparison** • None	**Critical outcomes** Reported at 18 weeks • Mortality • HRQL: fatigue severity (CIS), physical functioning (SF-36) • Steroid use reduction **Important outcomes** Reported at 18 weeks • Pulmonary function: VC % predicted; FEV1 % predicted; DLOC % predicted • Radiographic changes: ^{18}F-FDG PET (SUV_{max}) • Normalisation of calcium, lymphocytes, ACE and cytokine blood tests: ACE z-score, sIL-2R • SAE • AE leading to discontinuation
Vorselaars et al 2015 Prospective case series Nieuwegein, The Netherlands	• 56 patients with mixed sarcoidosis (pulmonary n= 34; cardiac n=2; SFN n=8; cutaneous n=4; CNS n=3) • 28 patients with pulmonary treatment indication reported separately	**Intervention** IFX IV 5 mg/kg at weeks 0 and 2, then every 4 weeks over a period of 6 months. Prednisone (19/56), dose tapered as required. **Comparison** • None	**Critical outcomes** Reported at 6 months • Mortality • HRQL (PGA; SF-36: physical functioning) • Steroid use reduction **Important outcomes** Reported at 6 months • Sarcoid disease activity • Organ-specific disease activity: pulmonary (FVC, FEV1, DLCOC, 6MWD) • Radiographic changes (SUVmax) • Normalisation of calcium, lymphocytes, angiotensin-converting enzyme (ACE) and cytokine blood tests: (ACE, ACE Z score, SIL-2R) • SAE • AE leading to discontinuation

Abbreviations
ACE: angiotensin-converting enzyme; AE: adverse events; CCS: corticosteroid; CIS: Checklist Individual Strength; CNS: central nervous system; DLCO: diffusing capacity of the lungs for carbon monoxide; EF: ejection fraction; ePOST: extrapulmonary Physician Organ Severity Tool; FEV1: forced expiratory volume in 1 second; ^{18}F-FDG PET (SUVmax): maximum standard uptake value on positron emission tomography (PET) using glucose analogue fluorine-18-labeled fluorodeoxyglucose (FDG); FVC: forced vital capacity; HRQL: Health-related quality of life; ICD: implantable cardioverter defibrillator; IFX: infliximab; IS: immunosuppressive agents; IV: intravenous; LVEF: left ventricular ejection fraction; OCRR: overall cutaneous response rate; PB: placebo; PGA: Patient Global Assessment; RCT: randomised controlled trial; SAE: serious adverse events; SD: standard deviation; SFN: small fibre neuropathy; SF-36: 36-item Short Form questionnaire; sIL-2R: soluble interleukin-2 receptor; SUVmax: maximum standard uptake value; VC: vital capacity; 6MWD: six-minute walking distance

5. Results

In people with refractory sarcoidosis[1], excluding neurosarcoidosis, what is the clinical effectiveness and safety of infliximab combined with current standard care (topical or systemic corticosteroids and /or at least one DMARD) compared with current standard care alone?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Mortality **Certainty of evidence:** Very low	Mortality 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. In total, one RCT and six case series reported mortality, with mean follow-up ranging from six weeks to 12 months. Mortality at six weeks • 1 RCT (Rossman et al 2006) of people with refractory pulmonary sarcoidosis reported mortality at six weeks. 1/13 (7.7%) people in the IFX group died, compared with 0/6 (0%) in the placebo (PB) group. Statistical significance was not reported. **(VERY LOW)** Mortality at 18 weeks • 1 case series of 45 people with refractory mixed sarcoidosis (van Rijswijk et al 2013) reported mortality at 18 weeks. 0/45 (0%) people in the study died. **(VERY LOW)** Mortality at six months • 1 case series of 56 people with refractory mixed sarcoidosis (Vorselaars et al 2015) reported mortality at six months. 1/56 (1.8%) died during the study and 1/56 died several months after treatment discontinuation (1.8%). **(VERY LOW)** Mortality at 12 months • Four case series of people with refractory cardiac sarcoidosis (Gilotra et al 2021, Harper et al 2019), cutaneous sarcoidosis (Heidelberger et al 2017) and mixed sarcoidosis (Sakkat et al 2022) reported mortality at up to 12 months. There were no deaths in the two cardiac sarcoidosis case series (0/38: Gilotra et al 2021; 0/36: Harper et al 2019), one death (1/46; 2.2%) in the cutaneous sarcoidosis case series, although it is not clear whether this person had IFX or another anti-TNF, and one death in the mixed sarcoidosis case series (1/33; 3.0%, Sakkat et al 2022). **(VERY LOW)** **These studies provide very low certainty evidence that the mortality rate in people treated with IFX for refractory sarcoidosis is 7.7% at six weeks (based on one death in a very small RCT); none of the six patients being treated with placebo died during this period. Six case series provided very low certainty evidence that the mortality rate for patients being treated with IFX for refractory sarcoidosis is 0% to 2% at up to six months and 0% to 3% at 12 months.**
Health-related quality of life (HRQL) **Certainty of evidence:** Very low to low	HRQL score is important to patients as it provides a holistic evaluation and indication of the patient's general health and perceived wellbeing.

[1] Refractory sarcoidosis is defined as sarcoid disease that has failed to respond to corticosteroids and/or at least one disease modifying anti-rheumatic drug (DMARD) as current standard care for sarcoidosis or where there is contra-indication or intolerance in treatment with those agents as current standard care for sarcoidosis. This also includes patients with stable disease that is maintained on unsustainable prolonged doses of steroids.

Outcome	Evidence statement
	One RCT and two case series reported HRQL, with follow-up ranging from six weeks to six months. Studies used the SF-36, the fatigue severity domain of the CIS, and the PGA score to measure HRQL[a]. HRQL at six weeks • 1 RCT (Rossman et al 2006) of 19 people with refractory pulmonary sarcoidosis reported HRQL at six weeks using the SF-36. There was a very small improvement in mean score from baseline (26.72±0.45) to six-week follow-up (27.11±0.46) in the IFX group; statistical significance was not reported. There was no change from baseline in the PB group (26.43±0.83 to 26.4±0.81). No between group comparison was reported. **(LOW)** HRQL at 18 weeks • One case series of 45 people with refractory mixed sarcoidosis (van Rijswijk et al 2013) reported: o a decrease of 5.3±8.5 points on the fatigue severity dimension of the CIS, indicating statistically significant improvement in fatigue (P= 0.003) **(VERY LOW)** o an increase of 12.6±23.9 points on the physical functioning domain of the SF-36, indicating improvement; P= 0.011. **(VERY LOW)** HRQL at six months • One case series of 56 people with refractory mixed sarcoidosis (Vorselaars et al 2015) reported: o a decrease of 14.6 points on the PGA score, indicating an improvement from baseline (P<0.0001). **(VERY LOW)** o an increase of 8.2 points on the physical functioning domain of the SF-36, indicating improvement (P=0.009). **(VERY LOW)** **The RCT provided low certainty evidence of a small improvement in HRQL compared to baseline at six weeks for people treated with IFX for refractory pulmonary sarcoidosis, but statistical significance was not reported. No between group comparison was reported. Two case series provided very low certainty evidence of statistically significant improvements compared to baseline in fatigue severity and physical functioning at 18 weeks to six months for people treated with IFX for refractory mixed sarcoidosis.**
Steroid use reduction **Certainty of evidence:** Very low	Steroid use reduction 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. Six case series reported steroid use at baseline and follow-up. Follow-up ranged from 18 weeks to 12 months. Steroid use reduction at 18 weeks • One case series of 45 people with refractory mixed sarcoidosis (van Rijswijk et al 2013) reported that there was no dose reduction. **(VERY LOW)** Steroid use at six months • Three case series (Gilotra et al 2021, Harper et al 2019, Vorselaars et al 2015) reported steroid use at six months. • Gilotra et al 2021 reported lower use of steroids at six-months (10.4±6.1 mg) compared with baseline in 38 people with refractory cardiac sarcoidosis (21.7±17.5 mg) (P=0.001). Harper et al 2019 reported a median (25^{th}-75^{th} percentile) dose of 20 mg (10-30 mg) at baseline in 35 people with refractory cardiac sarcoidosis, which reduced to 7.5 mg (2.5-15 mg) (P<0.01). Vorselaars et al 2015 reported a mean dose reduction of 8.8 mg among the 19 people with refractory mixed sarcoidosis taking prednisone at baseline (P=0.001)**. (VERY LOW)** Steroid use at 12 months • Four case series reported steroid use at 12 months (Gilotra et al 2021, Harper et al 2019, Heidelberger et al 2017, Sakkat et al 2022).

Outcome	Evidence statement
	• Gilotra et al 2021 reported lower use of steroids at six-months (7.3±7.3 mg) compared with baseline (21.7±17.5 mg) (P=0.002) in 38 people with refractory cardiac sarcoidosis. Harper et al 2019 reported a median (25^{th}-75^{th} percentile) dose of 20 mg (10-30 mg) at baseline, which reduced to 5 mg (0-10 mg) in the 29 people with refractory cardiac sarcoidosis available at 12-month follow-up (P<0.01). Heidelberger et al 2017 reported a reduction from 17.5 mg at baseline to 8.4 mg at last follow-up (up to 12 months) (P<0.001) in 46 people with refractory cutaneous sarcoidosis. Sakkat et al 2022 reported a reduction in mean daily dose from 21.7mg±12.7 at baseline to 10.5 mg±8.3 at 12 months (n=22 with mixed sarcoidosis). **(VERY LOW)** **Although one case series provided very low certainty evidence of no reduction in steroid use at 18 weeks, statistically significant reductions in steroid dose compared to baseline after six months (3 case series) and 12 months (4 case series) of treatment with IFX were reported for people with refractory sarcoidosis**, **with dose reductions in the region of 9 to 15mg per day.**
Important outcomes	
Sarcoid disease activity **Certainty of evidence:** Very low	Sarcoid disease activity is important to patients because it provides a method of measuring treatment response. Four case-series reported sarcoid disease activity as the number of responders following treatment with IFX, with follow-up at six to 12 months. Sarcoid disease activity at six months One case series of 56 people with refractory mixed sarcoidosis (Vorselaars et al 2015) calculated a composite overall response rate based on organ function, inflammatory activity and quality of life response. 40% had an excellent response, 39% a good response, 17% a partial response and 4% no response. **(VERY LOW)** Sarcoid disease activity at 12 months Three case series reported sarcoid disease activity at 12 months following treatment for refractory disease with IFX (Harper et al 2019, Heidelberger et al 2017, Sakkat et al 2022). • Harper et al 2019 described 24 of 36 (66.7%) people with refractory cardiac sarcoidosis as responders (20 of whom had steroid dose reduction, 12 improved dysrhythmia control and eight improved EF); nine people were described as non-responders (five of whom improved in at least one domain), and 3 remained stable. • Heidelberger et al 2017 described 31 of 46 (67.4%) people with refractory cutaneous sarcoidosis as responders (13 complete response, 18 partial response); 11 of 31 responders **(35%)** relapsed during treatment (8 during dose spacing or reduction of anti-TNF (n=3) or tapering of SS (n=3) or IS (n=2). • Sakkat et al 2022 stated that, of 11 people with refractory mixed sarcoidosis who discontinued treatment with IFX due to improvement or resolution of disease activity, seven relapsed. Median time to relapse: 8±2.04 months. **(VERY LOW)** **These studies provide very low certainty evidence that the majority of people (67% to 96%) treated with IFX for refractory were classified as having at least a partial response at six to 12 months, although definitions of response varied between studies and reduction in sarcoid disease activity was not maintained in 35% to 64% of responders.**
Organ-specific disease activity **Certainty of evidence:** Very low to low	Measures of organ-specific disease activity 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. In total, one RCT and six case-series provided data on organ-specific disease activity following treatment with IFX for refractory sarcoidosis. Follow-up ranged from six weeks to 12 months. Organ-specific activity included pulmonary function, upper

Outcome	Evidence statement
	airway function, cardiac function, cutaneous response, a general ePOST score for non-pulmonary sarcoidosis, peripheral lymph nodes, gastrointestinal function, uveitis and arthritis. Pulmonary function at six weeks • One RCT (n=19) (Rossman et al 2006) of 19 people with refractory pulmonary sarcoidosis reported VC as a measure of pulmonary function at six weeks: o a larger increase in % change from baseline expected VC in the IFX group (15.22±9.91%) vs the PB group (8.39±3.33%), although statistical significance was not reported for the change from baseline, and no between group comparison was reported. **(LOW)** o 2/13 IFX and 0/6 PB patients had a 15% improvement from baseline VC (no statistical significance reported for change from baseline, and no between group comparison reported). **(LOW)** o similar observed mean VC at baseline (2.47±0.2) and six weeks (2.65±0.19) in the IFX group, and in the PB group (2.37±0.31 at baseline; 2.40±0.28 at six weeks) (no between group statistical significance reported). **(LOW)** o an increase in % expected VC, from 59.63±3.69 at baseline to 64.68±3.60 in the IFX group, compared to an increase from 65.5±2.99 to 67.67±3.31 in the PB group (no between group statistical significance reported). **(LOW)** Pulmonary function at 18 weeks • One case series of 45 people with refractory mixed sarcoidosis (van Rijswijk et al 2013) reported statistically significant improvements compared to baseline for various measures: o % predicted FVC: +5.4±7.6 (P<0.0001) **(VERY LOW)** o % predicted FEV1: +5.3±8.3 (P<0.0001) **(VERY LOW)** o % predicted DLCO: +3.1±7.3 (P=0.012) **(VERY LOW)** Pulmonary function at six months • One case series of 56 people with refractory mixed sarcoidosis (Vorselaars et al 2015) reported improvements in various measures for a subgroup (n=28) with pulmonary treatment indication. o % predicted FVC: baseline: 73.6; change at 6 months: +6.6 (P=0.0007) **(VERY LOW)** o % predicted FEV1: baseline: 55.8; change at 6 months: +5.8 (P<0.0001) **(VERY LOW)** o % predicted DLCO: baseline: 56.6%; change at 6 months: +4.1 (P=0.001) **(VERY LOW)** o % predicted 6MWD: baseline: 61.0; change at 6 months: +4.2 (P value not reported) **(VERY LOW)** Pulmonary function at 12 months • One case series of 14 people with refractory mixed sarcoidosis (Sakkat et al 2022) reported change from baseline as: o FEV1: +90ml (55% increase) (95% CI -0.31 to 0.39)[b] **(VERY LOW)** o FVC: -20ml (0.77% decrease) (95% CI − 0.18 to 0.24) **(VERY LOW)** o % with treatment success (defined as an increase in absolute FVC or FEV1 by >10% or no change in FVC or FEV1 (± 10% from baseline): 78.6% (95% CI 49.2‑95.3) **(VERY LOW)** Cardiac function at six months • Two case series reported cardiac function at six months compared to baseline (Gilotra et al 2021, Harper et al 2019). • Gilotra et al 2021 reported that mean (SD) LVEF% changed from 52.6±15.9 (n=37) at baseline to 53.8±17.1 (n=26) at six months, based on FDG-PET findings (statistical significance not reported). They also reported no significant change in LVEF on ECG before and after treatment (from 45±16.5% to 47±15.0%; P=0.10; n=29). **(VERY LOW)**

Outcome	Evidence statement

	• Harper et al 2019 reported EF% as median (25th-75th percentile), with no change (P=0.43) from baseline 41 (32-55) (n=31) to six months 41 (35-54) (n=28). **(VERY LOW)**
	• Harper et al 2019 also reported ICD therapy use, reducing slightly from 4/25 (16%) at baseline to 2/23 (8.7%) at 6 months (statistical significance not reported) **(VERY LOW)**
	
	Cardiac function at 12 months
	• Two case series reported change in cardiac function from baseline to 12 months (Gilotra et al 2021, Harper et al 2019).
	• Gilotra et al 2021 reported that LVEF changed from 52.6±15.9 (n=37) at baseline to 49.3±16.1 (n=15) at 12 months (statistical significance not reported). **(VERY LOW)**
	• Harper et al 2019 reported ICD therapy use, reducing slightly from 4/25 (16%) at baseline to 2/16 (12.5%) at 12 months (P=0.45). This study did not report EF% at 12 months. **(VERY LOW)**
	
	Cutaneous sarcoidosis activity
	• One case series (n=46) (Heidelberger et al 2017) described the OCRR at 3, 12 and 6 months. The baseline value was not reported. **(VERY LOW)**
	  ○ 3 months: 24% (95% CI 14% to 40%)
	  ○ 6 months: 46% (95% CI 32% to 62%)
	  ○ 12 months: 79% (95% CI 64% to 98%)
	
	Cutaneous sarcoidosis activity at 12 months
	• Two case series described changes in cutaneous sarcoidosis at 12 months (Heidelberger et al 2017, Sakkat et al 2022).
	• Heidelberger et al 2017 reported that the median ePOST severity score (ranging from 0 to 6 for increasing severity) was 5 at baseline and 3 at last follow-up.
	• Sakkat et al 2022 defined treatment success as a 50% improvement in skin lesions in comparison to baseline images, with treatment success seen in 91.7% (61.5% to 99.8%) of the 12 people with cutaneous sarcoidosis in this study. **(VERY LOW)**
	
	Other organ-specific disease activity
	• One case series (Sakkat et al 2022) also reported treatment success rates following treatment with IFX, for other organs not already covered.
	  ○ upper airway (n=7): 71.5% (29.0% to 96.3%) had improvement in structural change on serial exam and imaging. **(VERY LOW)**
	  ○ peripheral lymph nodes (n=1): 100% (2.5% to 100%) had resolution of lymphadenopathy, based on clinical assessment. **(VERY LOW)**
	  ○ gastrointestinal sarcoidosis (n=1): 100 (2.5% to 100%) had resolution of symptoms and normalization of laboratory testing. **(VERY LOW)**
	  ○ uveitis (n=1): 100% (2.5% to 100%) had resolution of symptoms and improvement of abnormalities on serial eye exam. **(VERY LOW)**
	  ○ arthritis (n=1): 100% (2.5% to 100%) had resolution of symptoms and normalization of laboratory testing. **(VERY LOW)**
	
	For the population of people with refractory sarcoidosis, one RCT study presents low certainty evidence of improvements in pulmonary function in terms of % expected VC at six weeks following treatment with IFX. One case series and the subgroup of people with pulmonary indication in another case series provide very low certainty evidence of statistically significant improvements compared to baseline in % predicted FVC, FEV1 and DLCO at 18 weeks and 6 months, respectively, and the subgroup from one case series presents low certainty evidence of improvement from baseline 6MWD at six months (statistical significance not reported). Changes in pulmonary function

Outcome	Evidence statement
	did not appear to be significant at 12 months, although 78.6% were considered to have had treatment success at that time, (defined as an increase in absolute FVC or FEV1 by >10% or no change in FVC or FEV1 (± 10% from baseline). **In terms of cardiac function, very low certainty evidence suggests that compared to baseline, there were no statistically significant changes in LVEF, EF or ICD therapy use at six or 12 months.** **Very low certainty evidence from one case series reported that 24% of people treated with IFX for refractory cutaneous sarcoidosis responded at three months, rising to 46% at six months. At 12 months, results from two case series reported that the proportion of responders to IFX was between 79% and 92%.**
Radiographic changes **Certainty of evidence:** Very low to low	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. One RCT and six case series reported radiographic changes at follow-up ranging from six weeks to 12 months. Radiographic change at six weeks • One RCT (Rossman et al 2006) of 19 people with refractory pulmonary sarcoidosis reported radiologic improvement in 23% of 13 IFX patients compared with 0% of six PB patients. No statistical analysis was reported. **(LOW)** Radiographic change at 18 weeks • One case series (van Rijswijk et al 2013) reported ^{18}F-FDG PET (SUV_{max}) for 45 people with refractory mixed sarcoidosis. Mean±SD change from baseline was -2.7±3.4 (P< 0.00005) for pulmonary parenchyma and -2.3±3.4 (P<0.0005) for the mediastinum. **(VERY LOW)** Radiographic change at six months • One case series of 56 people with refractory mixed sarcoidosis (Vorselaars et al 2015) and one case series of 38 people with refractory cardiac sarcoidosis (Gilotra et al 2021) reported radiographic change at six months. • Vorselaars et al 2015 reported decreases in SUVmax of 2.97 (P<0.0001) for the mediastinum, 3.93 (P<0.0001) for the lung parenchyma and 5.76 (P<0.0001) for the lungs and index localisation (e.g. heart) in 49 patients with mixed refractory sarcoidosis. **(VERY LOW)** ○ Vorselaars et al 2015 reported mean change±SD from baseline 18F-FDG PET (SUVmax) to be -5.3±5.6 for lung parenchyma, -2.7±3.8 for the mediastinum and -5.5±5.6 for the index localisation in a subgroup of 28 patients with refractory pulmonary sarcoidosis. Statistical significance was not reported. **(VERY LOW)** • Gilotra et al 2021 reported that SUVmax values were 0.54±1.6 for 23 people with refractory cardiac sarcoidosis at six months, compared with 4.1±4.5 at baseline (n=34). **(VERY LOW)** Radiographic change at 12 months • One case series (Gilotra et al 2021) reported that SUVmax values were 0.65±1.5 for 11 people with refractory cardiac sarcoidosis at six months, compared with 4.1±4.5 at baseline (n=34). **(VERY LOW)** **These studies provide low certainty evidence of radiologic improvement at six weeks in people treated with IFX for refractory pulmonary sarcoidosis. There was very low certainty evidence from one case series for statistically significant improvements at 18 weeks for patients treated with IFX for**

Outcome	Evidence statement
	refractory mixed sarcoidosis. Very low certainty evidence was reported for statistically significant improvement in radiological changes from baseline to six months in people with refractory mixed sarcoidosis. One study presented improvement from baseline to six and 12 months in people with refractory cardiac sarcoidosis, but statistical significance was not reported.

Normalisation of calcium, lymphocytes, angiotensin-converting enzyme (ACE) and cytokine blood tests
 	
Certainty of evidence:
Very low
	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.
	
	Two case series reported change in ACE and serum sIL-2R, at 18 weeks and six months.
	
	ACE and serum sIL-2R at 18 weeks
	
	• One case series (van Rijswijk et 2013) reported a statistically significant reduction compared to baseline in serum ACE Z-score in 45 people with refractory mixed sarcoidosis: -2.01±3.31; P<0.0005. **(VERY LOW)**
	• van Rijswijk et al 2013 also reported a significant reduction compared to baseline in serum sIL-2R in 45 people with refractory mixed sarcoidosis: 2879±3755 pg/ml; P<0.00001. **(VERY LOW)**
	
	ACE and serum sIL-2R at 12 months
	• One case series (Vorselaars et al 2015) reported a significant decrease of serum ACE of 28.2 U/L (P=0.0003) from baseline in 49 patients with refractory mixed sarcoidosis. **(VERY LOW)**
	  ○ In a subgroup with pulmonary sarcoidosis (n=28), a reduction in serum ACE of 21.8±43.3 U/L compared to baseline was reported (statistical significance not reported). **(VERY LOW)**
	  ○ Vorselaars et al 2015 also reported a reduction in ACE Z-score of 1.78±3.33 compared to baseline in a subgroup with pulmonary sarcoidosis (n=28) (statistical significance not reported). **(VERY LOW)**
	• Vorselaars et al 2015 reported a significant decrease in serum sIL-2R (n=47) from baseline of 4269.4 pg/ml (P<0.0001). **(VERY LOW)**
	  ○ In a subgroup with pulmonary sarcoidosis (n=28), Vorselaars et al 2015 reported a reduction in serum sIL-2R from baseline of 3955±3883 pg/ml. **(VERY LOW)**
	
	Two case series provided very low certainty evidence of statistically significant reductions in ACE (either serum ACE or Z-value) and serum IL-2R compared to baseline. One of the case series also reported reductions in these markers for a subgroup of patients with pulmonary indication, but did not report statistical significance for these. None of the studies provided evidence for calcium, lymphocytes and cytokine blood tests.

Safety	
Presence of serious treatment-emergent adverse events (grade 3, 4 or 5) **Certainty of evidence:** Very low to low	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. One RCT and six case series reported data on adverse events, although serious treatment-emergent adverse events were not always distinguished from other adverse events. Adverse events at six weeks • One RCT (Rossman et al 2006) reported that 2/13 (15.4%) of the IFX group and 1/6 (16.7%) of the PB group had at least one AE at six weeks (1 IFX patient had right leg cellulitis; acute renal failure, pulmonary emboli, reoccurrence of cellulitis; 1 IFX patient had decreased white blood cell count and elevated creatine phosphokinase; 1 PB patient had shortness of breath). **(LOW)** Serious adverse events at 18 weeks

Outcome	Evidence statement
	• One case series (van Rijswijk et al 2013) reported that 1/45 (2.2%) people were hospitalised due to pneumonia, and 0/45 had tuberculosis. **(VERY LOW)** Serious adverse events at six months • One case series (Vorselaars et al 2015) reported that 3/56 (5.4%) people were hospitalised due to pneumonia and had to discontinue treatment. **(VERY LOW)** Serious adverse events and adverse events at 12 months • Four case-series reported a mixture of AE and SAE at 12 months. Gilotra et al 2021 reported 3 cases of shingles, 1 case of metapneumovirus pneumonia and one urinary tract infection. Harper et al 2019 reported one case of pneumonia pulmonary embolism, 1 case of c difficile diarrhoea, one case of shingles and one case of sepsis. Sakkat et al 2022 did not report SAE separately from AE. Heidelberger et al 2017 reported that 7/46 (15.2%) people were hospitalised for a grade 3 or 4 infection **(VERY LOW)** **Data on SAE were not generally presented clearly and separately from other AE. For people with refractory sarcoidosis**, **there was low certainty evidence of an AE rate of approximately 15% at six weeks, and very low certainty evidence that approximately 2% to 5% of people may experience an SAE at 18 weeks to six months. Very low certainty evidence suggests that around 15% of people on IFX may experience a grade 3 or 4 infection requiring hospitalisation at 12 months.**
Treatment-emergent adverse events leading to treatment discontinuation **Certainty of evidence:** Very low to low	One RCT and six case series reported data on discontinuations due to adverse events following treatment with IFX for refractory sarcoidosis. Discontinuations due to AE at six weeks • One RCT (Rossman et al 2006) reported that 15% of IFX vs 17% of PB patients discontinued treatment with IFX due to AE. **(LOW)** Discontinuations due to AE at 18 weeks • One case series (van Rijswijk et al 2013) reported that 1/45 (2.2%) discontinued due to AE. **(VERY LOW)** Discontinuations due to AE at six months • One case series (Vorselaars et al 2015) reported that 5/56 (8.9%) discontinued due to AE. **(VERY LOW)** Discontinuations due to AE at 12 months • Four case-series reported discontinuation rates due to AE of 2.6%, 2.8%, 24% and 21% (Gilotra et al 2021, Harper et al 2019, Heidelberger et al 2017, Sakkat et al 2022, respectively). **(VERY LOW)** **For people with refractory sarcoidosis**, **one RCT provided low certainty evidence of a 15% discontinuation rate at six weeks in the IFX group, with a similar rate (17%) of discontinuation in the PB group. There was very low certainty evidence from case series of discontinuation rates at 18 weeks to 12 months, ranging from approximately 2% to 24%.**

Abbreviations

ACE: angiotensin-converting enzyme; AE: adverse events; CIS: Checklist Individual Strength; DLCO: diffusing capacity of the lungs for carbon monoxide; ECG: electrocardiography; EF: ejection fraction; ePOST: extrapulmonary Physician Organ Severity Tool; FEV1: forced expiratory volume in 1 second; ^{18}F-FDG PET (SUVmax): maximum standard uptake value on positron emission tomography (PET) using glucose analogue fluorine-18-labeled fluorodeoxyglucose (FDG); FVC: forced vital capacity; HRQL: Health-related quality of life; ICD: implantable cardioverter defibrillator; IFX: infliximab; IS: immunosuppressive agents; LVEF: left ventricular ejection fraction; OCRR: overall cutaneous response rate; PB: placebo; PGA: Patient Global Assessment; RCT: randomised controlled trial; SAE: serious adverse events; SD: standard deviation; SF-36: 36-item Short Form questionnaire; sIL-2R: soluble interleukin-2 receptor; SS: systemic steroids; SUVmax: maximum standard uptake value; VC: vital capacity; 6MWD: six-minute walking distance

a. HRQL tools

Outcome	Evidence statement
• SF-36: physical functioning subscale or total score (physical and mental health subscales combined). 0-100 scale: lower scores indicate lower quality of life. • Checklist Individual Strength; fatigue severity dimension: higher scores indicate greater fatigue, cut-off score of 35 for severe fatigue. • Patient Global Assessment score: visual analogue scale 0-100, higher scores indicate lower quality of life. b. This is the confidence interval given in the paper, but it does not appear to include the difference of 90ml (55% increase).	

In people with refractory sarcoidosis, excluding neurosarcoidosis, what is the cost effectiveness of infliximab combined with current standard care (topical or systemic corticosteroids and /or at least one DMARD) compared with current standard care alone?

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 combined with current standard care (topical or systemic corticosteroids and /or at least one DMARD) more than the wider population of interest?

Outcome	Evidence statement

Subgroups
 	
Certainty of evidence:
 	
Very low
	Two case series (Heidelberger et al 2017; Vorselaars et al 2015) reported subgroup analyses.
	
	• Heidelberger et al 2017compared people with a skin-only indication for IFX (n=21) against those with visceral involvement (n=25).
	  ○ Baseline ePOST score was 5 in the skin-only indication group compared with 3 in the visceral involvement group (P<0.001), indicating more serious disease in the skin-only group. The study did not report the ePOST score for the subgroups at follow-up.
	  ○ There was a higher use of concomitant systemic steroids among people with a skin-only indication (18; 76%) compared with 7 (33%) of people with visceral involvement (P=0.003).
	  ○ There was little difference in the OCRR between subgroups (13 (62%) for skin-only vs 19 (72%) for visceral involvement; P=0.67).
	  ○ The number of infections was significantly lower among people with a skin-only indication compared with those with visceral involvement (2/21 (9.5%) vs 12/25 (48%), respectively; (P=0.02).
	• Vorselaars et al 2015 presented results for a subgroup of people with pulmonary indication for treatment. ACE was higher in people with extrapulmonary treatment indication (97.8 U/L) than for people with pulmonary indication (86.2 U/L).
	
	There was very limited information available on subgroups. Very low certainty evidence from one case series suggests that people with skin-only indications for IFX use may have fewer infections than those with visceral involvement, but they may be more likely to require concomitant systemic corticosteroids. There did not appear to be any difference in OCRR. However, baseline differences in ePOST score suggest that people with a skin-only indication may have had more severe disease before IFX initiation. Very low certainty evidence from one case series found that ACE was higher in people with extrapulmonary indication than for people with pulmonary indication.

Abbreviations ACE: angiotensin-converting enzyme; ePOST: extrapulmonary Physician Organ Severity Tool; IFX: infliximab; OCRR: overall cutaneous response rate	

From the evidence selected,

- what are the criteria used by the research studies to define refractory sarcoidosis?
- what were the loading dose, loading regime and ongoing schedule/dose used for infliximab?

Question	Evidence statement
What are the criteria used by the research studies to define refractory sarcoidosis?	The studies generally defined people with refractory sarcoidosis as those in whom previous treatment had failed, or who had serious adverse effects from corticosteroids/previous treatment (Rossman et al 2006; Heidelberger et al 2017). Van Rijswijk et al 2013 used a broader definition of previous medication that included corticosteroids, antimalarial drugs and methotrexate, and also commented that infliximab was given to people with unremitting disease activity (shown by elevated serum markers or increased uptake on PET scan). Vorselaars et al 2015 required people to be unresponsive to first- and second-line treatment, or to have experienced severe side-effects from these. Studies in cardiac sarcoidosis were more detailed, with Gilotra et al 2021 describing three scenarios under which TNF-α inhibitors would be offered: persistent cardiac inflammation despite immunosuppressive treatment; clinically active cardiac sarcoidosis defined by cardiac clinical events; intolerable side effects from immunosuppression regimens. Similarly, Harper et al 2019 defined refractory cardiac sarcoidosis as “progression of cardiac symptoms or cardiac involvement and failure of management with steroids and steroid sparing agents” Sakkat et al 2022 did not present exact criteria, simply referring to people with ‘biopsy-proven refractory sarcoidosis’.
What were the loading dose, loading regime and ongoing schedule/dose used for infliximab?	Studies generally reported use of IV IFX at a dose of 5mg/kg for the majority of patients. Three studies used a standard dosing schedule of 5mg/kg at weeks 0 and 2 (Rossman et al 2006), or at weeks 0 and 2 then every four weeks up to 18 weeks (van Rijswijk et al 2013) or six months (Vorselaars et al 2015). A slightly lower dose of 3 to 5mg/kg at weeks 0, 2 and 6 was reported by Sakkat et al 2022, followed by IFX every four to eight weeks for a variable duration that was individualised depending on clinical response, adverse events and the availability of funding. Most patients received 12 months of treatment, five completed 36 weeks. Harper et al 2019 used 5mg/kg of infliximab every four to six weeks with titration up to 10mg/kg for lack of response and lengthening of dosing interval to every eight weeks if the patient exhibited stability. 78% of participants had four-weekly dosing. Duration of treatment was unclear, but study stated that most received several years of IFX treatment; 35 of 36 patients completed at least six months and 29 completed at least one year of treatment. Gilotra et al 2021 mentions a “standard dosing frequency” and an average maximum dose of 6.1±2.2 (although 70% had a maximum dose of 5mg/kg). Treatment was for nine months, with a final follow-up 3 months after completion of IFX treatment. Heidelberger et al 2017: simply mentions “various regimen” and duration of treatment is not clear. The median (range) of follow-up was 45 (3 to 109) months.
Abbreviations IV: intravenous; IFX: infliximab; PET: positron emission tomography; TNF-α: tumour necrosis factor-alpha	

6. Discussion

This review considered the evidence for the clinical effectiveness, safety and cost effectiveness of infliximab (IFX) and current standard care in refractory sarcoidosis, excluding neurosarcoidosis, compared with current standard care. Critical outcomes of interest were mortality, health-related quality of life (HRQL) and reduction in steroid use. Other important outcomes were sarcoidosis disease activity; organ specific disease activity; radiographic changes; and normalisation of calcium, lymphocytes, angiotensin-converting enzyme (ACE) and cytokine blood tests. Evidence on safety included the presence of serious treatment-emergent adverse events (grade 3, 4 or 5), and treatment-emergent adverse events leading to treatment discontinuation. Cost effectiveness studies were also sought.

One comparative randomised controlled trial (RCT) was identified, but this was small and underpowered. It randomised 19 people to IFX or placebo at weeks 0 and 2, with follow-up at six weeks for the randomised phase. An open-label extension followed, which gave all participants two infusions at weeks 6 and 14, then followed them up for 24 weeks. This second phase study was not included as it was not comparative and was smaller than other included non-comparative case series. Early termination of enrolment mean that the study only included 19 of the planned 42 participants.

Evidence comes from this RCT, with further non-comparative evidence from six case series, which ranged in size from 33 to 56 people. One case series was described as a prospective open-label trial, and the other five were retrospective reviews of medical records in databases, disease registers or pharmacy records.

The majority of studies included used a dose of 5mg/kg intravenous IFX, although this could be increased in some studies. The shortest treatment duration was in the RCT (just two weeks), with other studies reporting a two-week initiation phase followed by a four-weekly dosing schedule. Follow-up in the case series ranged from 18 weeks to approximately 12 months. Given the nature of the data, i.e. case records from databases, follow-up time was not always clearly reported.

The RCT specifically included people with pulmonary sarcoidosis. There were two case series of people with cardiac sarcoidosis, one case series of people with cutaneous sarcoidosis (although approximately half of the patients also had visceral involvement), and three case series that included people with mixed sarcoidosis. Refractory sarcoidosis was generally defined as failure or lack of response on previous treatment (variously described as corticosteroids or immunosuppressants), or severe side-effects with such treatments.

The RCT and two of the case series were carried out in the USA, two of the case series were undertaken by the same institution in The Netherlands, one case series used a French database of people with sarcoidosis, and the remaining case series used case records from three centres in Canada and the UK.

All studies reported mortality, which ranged from 7.7% of the IFX arm (one person) in the six-week RCT (very low certainty evidence) to up to 2% at six months and 3% at 12 months (very low certainty evidence).

One RCT and two case series reported HRQL using the SF-36 (mainly just the physical functioning domain); the fatigue severity subdomain of the Checklist Individual Strength (CIS); and the Patient Global Assessment Score (PGA). The SF-36 has a 0-100 scale, with lower scores indicating lower quality of life; the fatigue severity dimension is one of four dimensions of the CIS; higher scores indicate greater fatigue and a cut-off score of 35 indicates severe fatigue. On the 0-100 scale of the PGA, higher scores indicate lower quality of life. None of the included

studies used disease specific measures to assess HRQL, for which the minimum clinically important differences (MCIDs) were defined in the PICO, so it is not clear how sensitive these more general measures would be for capturing any changes experienced by people with sarcoidosis. Compared to baseline, there was low certainty evidence of very small improvement in SF-36 score for people with pulmonary sarcoidosis at six weeks (statistical significance not reported), and very low certainty evidence of statistically significant improvements in fatigue severity and physical functioning at 18 weeks, and of improved PGA score and physical functioning at six months for people with mixed sarcoidosis.

Although there did not appear to be any reduction in steroid use at 18 weeks, there was very low certainty evidence from five case series of a statistically significant reduction in steroid dose after six and 12 months of treatment with IFX, with dose reductions in the region of 9 to 15mg per day.

Sarcoid disease activity was reported as 'response' by four case series, which defined this in different ways. There was very low certainty evidence that the majority of people treated with IFX were classified as having at least partial response at six to 12 months.

Organ-specific disease activity outcomes were reported most widely for pulmonary sarcoidosis, cardiac sarcoidosis and cutaneous sarcoidosis. The RCT reported low certainty evidence of improvements in percentage of expected vital capacity (VC) at six weeks, which was supported by very low certainty evidence of statistically significant improvements in % predicted forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and diffusing capacity of the lungs for carbon monoxide (DLCO) at 18 weeks (one case series) and six months (subgroup of people with pulmonary indication from one case series, which also reported improvements in the six-minute walking distance (6MWD) without statistical significance). Changes in pulmonary function did not appear to be significant at 12 months, although 78.6% were considered to have had treatment success at that time. There was no information on the clinical significance of any changes from baseline.

From the two case series that reported cardiac function, very low certainty evidence suggests that there were no statistically significant changes in left ventricular ejection fraction (LVEF) or ejection fraction (EF) and implantable cardioverter defibrillator (ICD) therapy from baseline to six or 12 months.

Very low certainty evidence from one case series indicates that only about 24% of people with cutaneous sarcoidosis were considered to have responded at three months, rising to 46% at six months. At 12 months, between 79% and 92% of people in two case series were considered to have responded to treatment successfully. However, there was variation in how this was measured, with one study reporting the overall cutaneous response rate (OCRR) based on ePOST scores (extrapulmonary Physician Organ Severity Tool, ranging from 0 (not affected) to 6 (very seriously affected)) and the other defining treatment success as at least a 50% improvement in baseline lesions compared with baseline images.

The RCT reported radiologic improvement in 23% of 13 people on IFX compared with none in the placebo group (low certainty evidence). Six case series reported radiographic change using ^{18}F-FDG PET (SUV_{max}), the maximum standard uptake value on positron emission tomography (PET) using the glucose analogue fluorine-18-labeled fluorodeoxyglucose (FDG), to give information about tissue glucose metabolism. There was very low certainty evidence of a significant improvement for pulmonary parenchyma and the mediastinum at 18 weeks six months, and improvements at 12 months (statistical significance not reported).

There was limited information available on normalisation of calcium, lymphocytes, angiotensin-converting enzyme (ACE) and cytokine blood tests. Two case series reported ACE and serum

soluble interleukin-2 receptor (sIL-2R), with very low certainty evidence of a reduction in these of approximately 1.8 to 2 Z scores for ACE and a reduction of between 2879 and 3955 pg/ml for serum IL-2R.

Reports of serious treatment-emergent adverse events were not always distinguishable from other adverse events. In the small RCT, there was low certainty evidence of an AE rate of approximately 15% at six weeks. Data from one case series offer very low certainty evidence that approximately 2% to 5% of people may experience an SAE at 18 weeks to six months. Very low certainty evidence from one case series suggests that around 15% of people on IFX may experience a grade 3 or 4 infection at 12 months.

Two case series reported subgroup analyses. One compared people with a skin-only indication for IFX against those with visceral involvement. Fewer people with skin-only involvement reported infections but they were more likely to require systemic steroids. There was no substantial difference between groups in OCCR at 12 months, although people with skin-only involvement had a higher mean baseline ePOST score, indicating more severe disease before IFX initiation, which may influence post-treatment results. The other case series reported that people with extrapulmonary indication had higher ACE levels than those with pulmonary treatment indication.

No evidence was identified for the cost effectiveness of IFX for refractory sarcoidosis.

A limitation of the evidence base is the non-comparative nature of the studies. There was only one RCT, which was small, underpowered, and of short duration. Only two doses of IFX were given during the randomised phase. The RCT did not present any effect estimates or statistical tests for comparisons between IFX and placebo, reporting results separately for each group. With the exception of one prospective case series, the other studies used retrospective analysis of clinical data. Selection bias may have affected data collection. A study of cardiac sarcoidosis patients mentioned that their own institution tended to see patients who were more severely ill or had worse response than those well enough to attend other cardiac centres. The French STAT study mentioned the voluntary nature of registration, which may also introduce bias.

In terms of the patients in the studies, a large proportion had mixed sarcoidosis refractory to steroids and/or DMARDS, and even those studies that focussed on particular organs (e.g. cardiac or skin) contained substantial proportions of people with multiple organ involvement. It is not clear whether or not this may affect response to IFX treatment or patient outcomes. Whilst the mean age of patients in all studies was similar (approximately 50 years old), the length of time they had had sarcoidosis/severity of disease varied or was not reported in a way that allowed comparisons across studies.

In addition to being downgraded for lack of a comparator group, GRADE ratings of four case series were further downgraded for indirectness due to their inclusion of between 14% and 33% of people who had central nervous system involvement or small fibre neuropathy, as neurosarcoidosis was out of scope for this review. Outcomes were downgraded if they were not reported separately for people who did not have neurosarcoidosis.

Two case series also received a downgrade for indirectness as 13% and 21% of their patients did not receive IFX, but instead had adalimumab or etanercept. Outcome data were not available separately for those who had IFX.

The reporting of adverse events was not clear in many of the studies, making it difficult to distinguish treatment-emergent serious adverse events from other adverse events. The retrospective records-based nature of the majority of the studies means that there may be some ambiguity in the reporting of these, particularly where timescales of follow-up are unclear.

One study reported use of ICD therapy (Harper et al 2019), which is not necessarily the same as the number of people in need of ICD therapy (as specified in the PICO) and could have been impacted by resource availability or other issues.

7. Conclusion

This review included one RCT and six case series which provide very low to low certainty evidence on critical and important outcomes for the use of infliximab for people with refractory sarcoidosis, compared to current standard care.

The only RCT was small (n=19) and underpowered, and did not provide statistical comparisons of outcomes for infliximab compared to placebo. The majority of the evidence base is therefore non-comparative and consequently of very low certainty.

Mortality was reported by all studies, with one death in the RCT and a mortality rate of 2% to 3% over longer follow-ups. Studies longer than 12 months would be helpful for capturing any differences in mortality rate.

No studies reported disease-specific measures of HRQL. There was no evidence of any improvement in general HRQL in the short RCT, but very low certainty evidence from two case series reported that fatigue and physical functioning may improve with longer-term treatment. Although one 18-week case series did not indicate any substantial reduction in steroid use, five longer-term case series suggested dose reductions at up to 12 months.

In terms of sarcoid disease activity, there was very low certainty evidence that the majority of people treated with IFX were classified as having at least partial response at six to 12 months, although definitions of response varied between studies. Low to very low certainty evidence indicates improvements in measures of pulmonary function at six months, but there was little evidence for change in cardiac function. Very low certainty evidence suggests cutaneous sarcoidosis may respond to IFX with treatment beyond six months, but methods for assessing this are of unknown reproducibility.

Although none of the case series reported if treatment effects reached clinically significant proportions or offered significant benefit to patients, there was very low certainty evidence of statistically significant changes from baseline for reduced steroid dose, improved fatigue and physical function, and the majority of patients had at least a partial response to treatment with IFX.

The evidence base for this review was of very low certainty due to its broadly non-comparative nature. It is therefore not possible to reach any conclusions about how infliximab compares to standard care for the treatment of people with refractory sarcoidosis, excluding neurosarcoidosis.

No evidence was available for the cost effectiveness of infliximab for sarcoidosis.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with refractory sarcoidosis, excluding neurosarcoidosis, what is the clinical effectiveness of infliximab combined with current standard care compared with current standard care alone?
2. In people with refractory sarcoidosis, excluding neurosarcoidosis, what is the safety of infliximab combined with current standard care compared with current standard care alone?
3. In people with refractory sarcoidosis, excluding neurosarcoidosis, what is the cost-effectiveness of infliximab combined with current standard care compared with current standard care alone?
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 refractory 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 refractory sarcoidosis affecting any organ or system except the neurological system who have had an inadequate response to current standard care. [Refractory sarcoidosis is defined as sarcoid disease that has failed to respond to corticosteroids and/or at least one disease modifying anti-rheumatic drug (DMARD) as current standard care for sarcoidosis or where there is contra-indication or intolerance in treatment with those agents as current standard care for sarcoidosis. This would also include patients with stable disease that is maintained on unsustainable prolonged doses of steroids (as defined by the authors.)] [Infliximab is already routinely commissioned for patients with refractory isolated neurosarcoidosis and those with systemic sarcoidosis with refractory, magnetic resonance imaging (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 in combination with current standard care (topical or systemic corticosteroids and /or at least one DMARD)
C – Comparator(s)	Current standard care [Topical or systemic corticosteroids and/or at least one DMARD (methotrexate, hydroxychloroquine, azathioprine, mycophenolate, leflunomide or cyclophosphamide).]
O – Outcomes	**Clinical Effectiveness**

	Response to treatment would be expected to be achieved within 6 months of starting treatment. Minimum clinically important differences (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.* <u>*Important to decision-making:*</u> • **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.* o ***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. **Safety** • 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. **Cost effectiveness**
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	2006-2022 (major randomised control trials were from 2006 onwards (Baughman et al.,2006, Rossman et al.,2006, Judson et al.,2008 and Baughman et al.,2016)
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language from 2006 onwards. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 1 January 2006 to 11 August 2022

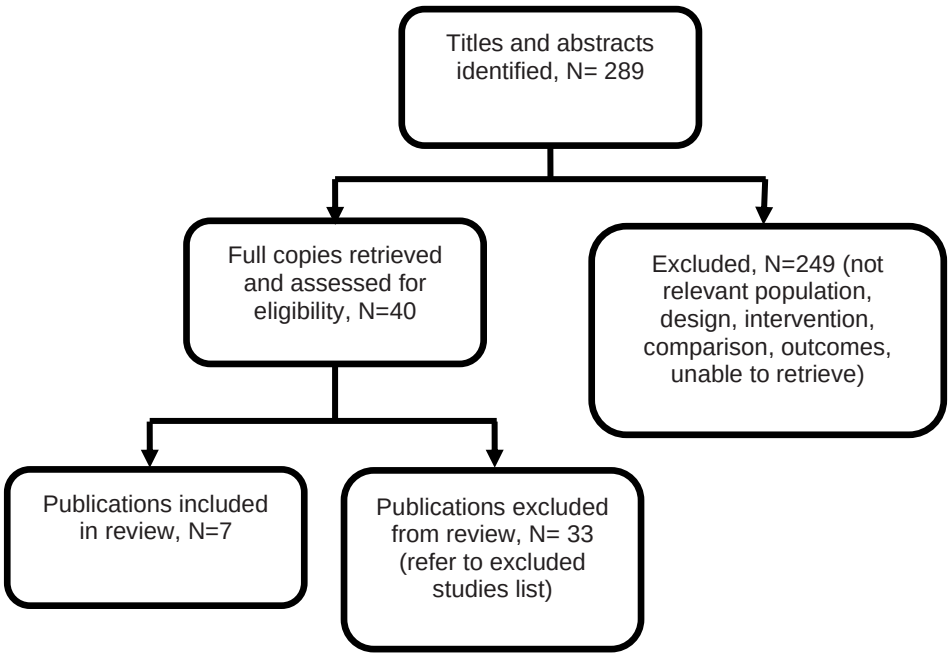
Medline search

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 literature searches identified 289 references. These were screened using their titles and abstracts and 40 references were obtained in full text and assessed for relevance. Of these, 7 references are included in the evidence summary. The remaining 33 references were excluded and are listed in Appendix D.

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 included a mixture of studies, some of which did not meet the PICO for this review. Pooled data not available for studies of interest, so the individual studies were considered for inclusion separately.
Sakkat, A. et al., 2022. Infliximab therapy in refractory sarcoidosis: A multicenter real-world analysis. Respiratory Research, 23(1).	Included
Full evidence summary | Refractory extrapulmonary sarcoidosis: infliximab | Advice | NICE. [online] Available at: https://www.nice.org.uk/advice/es4/chapter/Fullevidence-summary#relevance-to-nice-guidance-programmes.	Excluded. Not a systematic review, and included a mixture of studies, some of which did not meet the PICO for this review.

Appendix D Excluded studies table

Study reference	Reason for exclusion
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.	Conference abstract
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.	Includes a mix of irrelevant studies and ones which are in scope, so preferable to focus on the individual studies.
Aguiar M, Marcal N, Mendes AC, Bugalho de Almeida A. Infliximab for treating sarcoidosis patients, Portuguese experience. Rev Port Pneumol. 2011;17(2):85-93.	Paper not in English
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.	n<30, larger case series included
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.	n<30, larger case series included
Banse C, Bisson-Vaivre A, Kozyreff-Meurice M, Vittecoq O, Goeb V. No impact of tumor necrosis-factor antagonists on the joint manifestations of sarcoidosis. Int J Gen Med. 2013;6:605-11.	n<30, larger case series included
Barba T, Marquet A, Bouvry D, Cohen-Aubart F, Ruivard M, Debarbieux S, et al. Efficacy and safety of infliximab therapy in refractory upper respiratory tract sarcoidosis: Experience from the STAT registry. Sarcoidosis Vasculitis and Diffuse Lung Diseases. 2017;34(4):343-51.	n<30, larger case series included
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.	Not clear that all infliximab patients were refractory to corticosteroids with/without Disease Modifying Anti-Rheumatic Drugs.
Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, du Bois R, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med. 2006;174(7):795-802.	Population does not meet PICO. This RCT (and related studies) did not include patients who had failed to respond to CCS+/- DMARD and therefore did not meet the Population definition of refractory in the PICO in Appendix A.
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.	Population does not meet PICO. This was a subset from the Baughman 2006 RCT, so did not include patients who had failed to respond to CCS+/- DMARD and therefore did not meet the Population definition of refractory disease in the PICO in Appendix A.
Baughman RP, Lower EE, Ingledue R, Kaufman AH. Management of ocular sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2012;29(1):26-33.	n<30, larger case series included
Doty JD, Mazur JE, Judson MA. Treatment of Sarcoidosis With Infliximab. Chest. 2005;127(3):1064-71.	n<30, larger case series included

Study reference	Reason for exclusion
Elfferich MD, Nelemans PJ, Ponds RW, De Vries J, Wijnen PA, Drent M. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF-alpha treatment. Respiration. 2010;80(3):212-9.	Data for infliximab not available separately
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.	No pooled result for population of interest
Hostettler KE, Studler U, Tamm M, Brutsche MH. Long-term treatment with infliximab in patients with sarcoidosis. Respiration. 2012;83(3):218-24.	n<30, larger case series included
Jamilloux Y, Cohen-Aubart F, Chapelon-Abric C, Maucort-Boulch D, Marquet A, Perard L, et al. Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: A multicenter study of 132 patients. Semin Arthritis Rheum. 2017;47(2):288-94.	n<30, larger case series included
Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH, Kavuru MS, et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. Eur Respir J. 2008;31(6):1189-96.	Population does not meet PICO. This was a subset from the Baughman 2006 RCT, so did not include patients who had failed to respond to CCS+/- DMARD and therefore did not meet the Population definition of refractory disease in the PICO in Appendix A.
Keijsers RG, Verzijlbergen JF, van Diepen DM, van den Bosch JM, Grutters JC. 18F-FDG PET in sarcoidosis: an observational study in 12 patients treated with infliximab. Sarcoidosis Vasc Diffuse Lung Dis. 2008;25(2):143-9.	n<30, larger case series included
Kullberg S, Rivera NV, Abo Al Hayja M, Grunewald J, Eklund A. Changes in lung immune cells related to clinical outcome during treatment with infliximab for sarcoidosis. Clin Exp Immunol. 2020;201(1):85-93.	n<30, larger case series included which reported the outcomes specified in the PICO in Appendix A.
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.	n<30, larger case series included
Lower EE, Sturdivant M, Grate L, Baughman RP. Use of third-line therapies in advanced sarcoidosis. Clin Exp Rheumatol. 2020;38(5):834-40.	Up to 118/258 patients treated with infliximab had central nervous system involvement. More direct studies available.
Marquet A, Chapelon-Abric C, Maucort-Boulch D, Cohen-Aubart F, Perard L, Bouillet L, et al. Efficacy and safety of TNF antagonists in ocular sarcoidosis: Data from the French registry STAT. Sarcoidosis Vasculitis and Diffuse Lung Diseases. 2017;34(1):74-80.	Only 14 pts on infliximab, larger case series included
Ramos-Casals M, Brito-Zeron P, Munoz S, Soto MJ, Group BS. A systematic review of the off-label use of biological therapies in systemic autoimmune diseases. Medicine (Baltimore). 2008;87(6):345-64.	Superseded by more recent systematic review
Riancho-Zarrabeitia L, Calvo-Rio V, Blanco R, Mesquida M, Adan AM, Herreras JM, et al. Anti-TNF-alpha therapy in refractory uveitis associated with sarcoidosis: Multicenter study of 17 patients. Semin Arthritis Rheum. 2015;45(3):361-8.	Small case series, not required to include all sarcoid sites
Russell E, Luk F, Manocha S, Ho T, O'Connor C, Hussain H. Long term follow-up of infliximab efficacy in pulmonary and extra-pulmonary sarcoidosis refractory to	n<30, larger case series included

Study reference	Reason for exclusion
conventional therapy. Semin Arthritis Rheum. 2013;43(1):119-24.	
Saleh S, Ghodsian S, Yakimova V, Henderson J, Sharma OP. Effectiveness of infliximab in treating selected patients with sarcoidosis. Respir Med. 2006;100(11):2053-9.	n<30, larger case series included
Shah P, Bechman K, Galloway J. The evidence for biologic immunotherapy in Sarcoidosis: A systematic review. Australasian Medical Journal. 2017;10(9):829-37.	Superseded by more recent systematic review
Stagaki E, Mountford WK, Lackland DT, Judson MA. The treatment of lupus pernio: results of 116 treatment courses in 54 patients. Chest. 2009;135(2):468-76.	Larger study included that has more patients with cutaneous sarcoidosis
Sweiss NJ, Barnathan ES, Lo K, Judson MA, Baughman R, Investigators T. C-reactive protein predicts response to infliximab in patients with chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010;27(1):49-56.	Population does not meet PICO. This was a secondary analysis of data from the Baughman 2006 RCT, so did not include patients who had failed to respond to CCS+/-DMARD and therefore did not meet the Population definition of refractory disease in the PICO in Appendix A.
Wade S, Carruthers M. Tumor necrosis factor inhibitors for sarcoidosis. Arthritis and Rheumatology. 2017;69(Supplement 10).	Conference abstract
Wade S, Carruthers M. Tumor necrosis factor inhibitors for sarcoidosis. J Rheumatol. 2018;45(7):1019.	Conference abstract
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.	n<30, larger case series included
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.	Population does not meet PICO. Only n=17 with sarcoidosis, not necessarily refractory. Larger case series included.

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Intervention	Study outcomes	Appraisal and funding
Rossman MD, Newman LS, Baughman RP, Teirstein A, Weinberger SE, Miller W, Jr., et al. A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2006;23(3):201-8. **Study location** 5 sites in USA **Study type** RCT (randomised phase 6 weeks; open-label extension for all patients not extracted) **Study aim** To demonstrate safety, tolerability and efficacy of IFX for people with active pulmonary sarcoidosis. **Study dates** January 2002 to December 2003	**Inclusion criteria** Stage II, III or IV chest radiograph indicating pulmonary parenchymal involvement; vital capacity ≤.50% and ≤80% predicted; previous or current treatment with corticosteroids with a need for institution of another agent based on either suboptimal response to or intolerance of corticosteroids; (for those on oral corticosteroids) stable dose of prednisone up to 60mg/d (or other equivalent corticosteroid) for at least 2 weeks **Exclusion Criteria** Arterial pO2 ≤55mg Hg at rest or with oxygen saturation by pulse oximetry ≤ 88% at rest; severe, progressive or uncontrolled renal, hepatic, hematologic, endocrine, cardiac or neurologic disease; taking immunosuppressive	**Interventions** IFX 5mg/kg at weeks 0 and 2 **Comparators** PB at weeks 0 and 2 **Concomitant corticosteroids** n taking (%); dose, mean mg±SD; duration, mean days±SD IFX: 9 (69.2%); 23.78±3.74; 850±319 PB: 4 (66.7%); 8.0±2.27; 335±38 **Follow-up** 6 weeks (randomised phase)	**Critical outcomes** **Mortality (6 weeks)** IFX vs PB: 1/13 vs 0/6 **HRQL** SF36 (baseline) IFX vs PB: 26.72±0.45 vs 26.43±0.83 SF36 (week 6) IFX vs PB: 27.11±0.46 vs 26.4±0.81 **Important outcomes** **Organ-specific disease activity** **Pulmonary function – vital capacity** Percent change in expected vital capacity (baseline to week 6) IFX vs PB: 15.22±9.91% vs 8.39±3.33% VC_{obs} (baseline) IFX vs PB: 2.47±0.2 vs 2.37±0.31 VC_{obs} (6 weeks) IFX vs PB: 2.65±0.19 vs 2.40±0.28 $VC\%_{exp}$ (baseline)	This study was appraised using the Cochrane RoB1 checklist for RCTs. 1. Unclear 2. Unclear 3. Low 4. Low 5. Low 6. Unclear 7. High **Source of funding:** Supported by a grant from Centocor Inc. **Other comments:** Trial recruitment ended early, so only 19/42 planned participants were enrolled and the study is underpowered. Outcomes are reported as IFX vs PB, with no between-group comparisons or statistical tests reported. Only 2 IFX infusions were given during the randomised phase, and follow-up was short.

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	agents in previous 4 weeks **Total sample size** 19 enrolled out of a planned 42 **No. of participants in each treatment group** IFX : n=13 PB: n=6 **Baseline characteristics** IFX vs PB: Age: 46.8±2.3 vs 49.3±4.9 Male: 5 (38.5) vs 5 (83.3) Race Caucasian: 8 (61.45) vs 3 (50.0) Black: 5 (38.46) vs 3 (50.0) FVC_1: 50.6±4.4 vs 56.8±5.2 Scadding Radiographic Stage II: 7 (53.8) vs 4 (66.7) III: 6 (46.15) vs 1(16.7) IV: 0 (0) vs 1 (16.7)		IFX vs PB: 59.63±3.69 vs 65.5±2.99 $VC\%_{exp}$ (6 weeks) IFX vs PB: 64.68±3.60 vs 67.67±3.31 15% improvement in VC (6 weeks) IFX vs PB: 2/13 vs 0/6 **Radiographic changes** Radiologic improvement (6 weeks) IFX vs PB: 23.0% vs 0% **AE (days 1-42 since treatment initiation)** IFX vs PB: 1 or more AE: 2/13 vs 1/6 right leg cellulitis; acute renal failure, pulmonary emboli, cellulitis (all 3): 1/13 vs 0/6 decreased white blood cell count and elevated creatine phosphokinase: 1/13 vs 0/6 Severe shortness of breath: 0/13 vs 1/6 **AE leading to discontinuation** Discontinuations (reasons not given) IFX vs PB: 15% vs 17%	
Gilotra NA, Wand AL, Pillarisetty A, Devraj M, Pavlovic N, Ahmed S, et al. Clinical and Imaging	**Inclusion criteria** Treated for CS with a TNF alpha inhibitor in	**Interventions** IFX IV infusion at standard dosing frequency with weight-	**Critical outcomes** **Mortality**	This study was appraised using the JBI checklist for case-series.

Study details	Population	Intervention	Study outcomes	Appraisal and funding
Response to Tumor Necrosis Factor Alpha Inhibitors in Treatment of Cardiac Sarcoidosis: A Multicenter Experience. Journal of Cardiac Failure. 2021;27(1):83-91. **Study location** USA **Study type** Retrospective case series (from 2 institutions' Cardiac Sarcoidosis Registries) **Study aim** To describe the safety and efficacy of biologic agents, with a focus on TNF alpha inhibitors and FDG-PET responsiveness, in a multicenter cohort of patient with CS **Study dates** 2014 **-** 2019	consultation with a sarcoidosis specialist and cardiologist. Extracardiac organ involvement was determined using World Association of Sarcoidosis and Other Granulomatous Diseases criteria.[12] CS diagnosed on Heart Rhythm Society (HRS) criteria or Japanese imaging criteria. Patients were included if they underwent treatment with TNF alpha inhibitor therapy specifically for cardiac involvement of their sarcoidosis. Treatment with TNF alpha inhibitors reserved for (1) persistent cardiac inflammation on FDG-PET despite immunosuppressive treatment (n=22) (2) clinically active CS defined by cardiac clinical events (i.e., cardiomyopathy, arrhythmia or conduction abnormalities), (n=13) and/or (3) intolerable side effects from	based dosing: mean±SD dose (mg/kg): 6.1±2.2 21/30 (70%) had 5mg/kg Prednisone use: n = 33/38 (mean dose 21.7±17.5 mg) **Comparators** No comparator. **Follow-up** **Approx. 6 months** **Approx. 12 months**	N=0 **Steroid use reduction** Mean±SD dose Baseline: 21.7±17.5 mg 6 months: 10.4±6.1 mg (P=0.001) 12 months: 7.3±7.3 mg (P=0.002) **Important outcomes** **Organ-specific disease activity** **Cardiac** function, LVEF, %, measured on FDG-PET Baseline: 52.6±15.9 (n = 37) 6 months: 53.8±17.1 (n = 26) 12 months: 49.3±16.1 (n = 15) *Individual events (LVAD, heart transplant, ICD treatment) mentioned in text, but not clear whether recipients had IFX or adalimumab.* LVEF measured on ECG (n=29) Baseline: 45±16.5% 12 months: 47±15.0%; P=0.10 **Radiographic changes,** SUVmax Baseline: 4.1±4.5 (n = 34) 6 months: 0.54±1.6 (n = 23) 12 months: 0.65±1.5 (n = 11)	1. Yes 2. Yes 3. Yes 4. No information 5. No information 6. Yes 7. Yes 8. No 9. Yes 10. Yes **Other comments:** As a case series, this study does not have a comparator. Where possible (e.g. AE), data are reported for IFX patients only, but most data not available separately. Whilst the majority (30/38) had IFX, it is not clear how this affects outcomes. Only treatment indications 1 and 3 appear to relate to the standard definition of refractory sarcoidosis. It is not clear how many people only had indication 2, as 14 people had multiple indications. Follow-times are approximate, as they were based on timings of second and third PET scans. The study used data from 2 large sarcoidosis centres, so may not be generalisable to other settings.

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	immunosuppression regimens. (n=17) (n=14 had multiple indications) **Exclusion Criteria** Not reported **Total sample size** N = 30 IFX (8 had adalimumab) Total study n = 38 **Baseline characteristics** Mean±SD age (yrs): 49.9±9.5 22 (58%) male 20 (53%) African American, 18 (47%) White Ventricular arrhythmia: 13 (34%) Atrial fibrillation: 4(11%) Atrioventricular block: 10 (26.3%) Atrioventricular block: 10 (26.3%) Heart failure: 13 (34%) LVEF, % 48.5 (15)		**SAE (during treatment)** Shingles (n=3) Metapneumovirus pneumonia (n=1) Urinary tract infection (n=1) **AE leading to discontinuation** 1 intra-abdominal collection presumed to be infectious, required discontinuation of IFX for 4 months	**Source of funding:** "Disclosures: none"
Harper LJ, McCarthy M, Ribeiro Neto ML,	**Inclusion criteria**	**Interventions**	**Critical outcomes**	This study was appraised using the JBI checklist for case series.

Study details	Population	Intervention	Study outcomes	Appraisal and funding
Hachamovitch R, Pearson K, Bonanno B, et al. Infliximab for Refractory Cardiac Sarcoidosis. Am J Cardiol. 2019;124(10):1630-5. **Study location** Retrospective review of records, investigators' institution in Cleveland Clinic, USA **Study type** Retrospective case series **Study aim** To evaluate the safety and efficacy of IFX in cardiac sarcoidosis patients. **Study dates** Not reported	All patients who had ICD-10 coding for cardiac myocarditis (D86.85, defined according to WASOG criteria) and had an order placed at any point for IFX. Institution practice is to initiate IFX for patients with refractory cardiac sarcoidosis, defined as progression of cardiac symptoms or cardiac involvement and failure of management with steroids and steroid sparing agents. **Exclusion Criteria** People started on IFX <6 months before analysis, or if IFX was initiated for noncardiac manifestations of sarcoidosis. **Total sample size** N=36 **Baseline characteristics** Age (years) 50±11 Male 26 (72%) White 28 (78) Black 8 (22) Organ systems involved	5 mg/kg of IFX every 4 to 6 weeks with titration up to 10 mg/kg for lack of response and lengthening of dosing interval to every 8 weeks if the patient exhibited stability. Most patients received several years of IFX treatment. 35 patients completed at least 6 months and 29 completed at least 1 year of IFX. Steroid use at IFX initiation: 32 (89%) **Comparators** No comparator. **Follow-up** 6 months 12 months	**Mortality** N=0 **Steroid use reduction** Dose (mg/day), median (25^{th}-75^{th}) Baseline: 20 (10 to 30) (n=35) 6 months: 7.5 (2.5 to 15) (n=35) 12 months: 5 (0 to 10) (n=29) P<0.01 for reduction **Important outcomes** **Sarcoid disease activity** • Responder: 24/36 (20 had steroid dose reduction; 12 had improved dysrhythmia control; EF improved in 8) • Non-responder: 9/36 (although 5 had improvement in at least 1 domain; 2 received heart transplants) • Stable: 3/36 **Organ-specific disease activity** **Cardiac function** Ejection fraction (%), median (25^{th} to 75^{th}) Baseline: 41 (32 to 55) (n=31) 6 months: 41 (35 to 54) (n=28) 12 months: NA P=0.43 for change to 6 months ICD therapy: n (%) Baseline: 4/25 (16%) 6 months: 2/23 (8.7%) 12 months: 2/16 (12.5%) P=0.45 for change to 12 months	1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:** As a case series, this study does not have a comparator. 12/36 participants had neurosarcoidosis so do not meet the PICO for this review; data are not available separately for those without neurological involvement. Study authors mention that LVEF and PET scan data were not available for people who received cardiac care at other centres (generally those doing well), which may have underestimated treatment effect. Paper reports the number of people having ICD therapy, rather than the number who may require it. **Source of funding:**

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	• Heart 36 (100%) • Lung 26 (72%) • Neurologic 12 (33%) • Skin 7 (19%) • Bone 3 (8%) • Ocular 2 (6%) • Liver 2 (6%) • Kidney 1 (3%) • Gastrointestinal 1 (3%) • Spleen 1 (3%) Ejection fraction <30% 6 (17%) Ventricular tachycardia 8 (22%) High-grade heart block 7 (19%) Biventricular pacing 4 (11%)		**SAE** N= 4/36 had adverse events but continued: • Pneumonia pulmonary embolism (n=1) • C. difficile diarrhoea (n=1) • Shingles (n=1) • Sepsis (n=1) **AE leading to discontinuation** • Disseminated cryptococcus (n=1) • Decompensation of heart failure (thought to be secondary to severity of cardiac sarcoidosis and not due to IFX therapy by treating physicians.) (n=1)	No study funding mentioned (case review). None of the authors have any financial interests to disclose.
Heidelberger V, Ingen-Housz-Oro S, Marquet A, Mahevas M, Bessis D, Bouillet L, et al. Efficacy and Tolerance of Anti-Tumor Necrosis Factor alpha Agents in Cutaneous Sarcoidosis: A French Study of 46 Cases. JAMA Dermatol. 2017;153(7):681-5. **Study location** France **Study type**	**Inclusion criteria** • histologically proven sarcoidosis made in accordance with the guidelines of the World Association of Sarcoidosis and Other Granulomatous diseases, • age > 18 years • current or previous treatment with anti-TNF (initiation of anti-TNF therapy decided by the referral physician) • skin involvement	**Interventions** IFX: 40 (87%) Adalimumab: 5 (11%) Etanercept: 1 (2%) Anti-TNF administered with SS (mean dose of prednisone of 17.5 mg/d) in 28 cases (61%) and IS (methotrexate n=26) in 32 cases (69.5%). **Comparators** No comparator.	**Critical outcomes** **Mortality** 1 person treated with concomitant prednisone and azathioprine died of pneumonitis. *Not clear whether this patient had IFX or another anti-TNF.* **Steroid use reduction** Baseline Mean dose: 17.5 mg/d Last follow-up Mean dose: 8.4 mg/d (P<0.001 for change from baseline) **Important outcomes**	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. No 8. Yes 9. Yes 10. Yes

Study details	Population	Intervention	Study outcomes	Appraisal and funding
Review of cases in STAT (Sarcoidosis Treated with Anti-TNF): a French retrospective and prospective multicenter observational database. **Study aim** To assess the long-term efficacy and safety of anti-TNF in treating cutaneous sarcoidosis. **Study dates** January 2004 - January 2016	**Exclusion Criteria** Not reported. **Total sample size** N=46 **Baseline characteristics** Median (range) age: 50 (14-78) 13/46 (28%) male Geographical origin: Caucasian: 14 (30%) Northern African 14 (30%) Caribbean 9 (20%) African 6 (13%) Median (range) organs involved: 3 (1-8) 7 (17%) had CNS involvement Type of cutaneous lesions, n (%) Lupus pernio: 21 (40) Nodules (small and large): 20 (43) Plaques 11 (24) Other: 6 (12) Localisation, n (%) Face and neck: 33 (69) Trunk and limbs: 22 (48)	Primary analysis: efficacy and safety in whole cohort Secondary analysis: compared patients with a skin-only indication for anti-TNF (Group 1, n=21) and patients treated for visceral involvement (Group 2, n=25). **Follow-up** **3 months** **6 months** **12 months**	**Sarcoid disease activity** • Responder: 31/46 (13 complete response, 18 partial response) • 11/31 responders relapsed during treatment, 8 due to dose spacing/reduction of anti-TNF (n=3) or tapering of SS (n=3) or IS (n=2 (later rectified). Anti-TNF definitively discontinued in 3 **Organ-specific disease activity** **Overall cutaneous response rate** 3 months: 24% (95% CI 14% to 40%) 6 months: 46% (95% CI 32% to 62%) 12 months: 79% (95% CI 64% to 98%) Median ePOST severity score Baseline: 5 Last follow-up: 3 **Subgroup analysis** Group 1: skin-only indication vs group 2: visceral involvement Baseline ePOST score: 5 vs 3; P< 0.001) (not reported at follow-up) Use of concomitant SS (18 [76%] vs 7 [33%]; P=0.003) OCRR: (13 [62%] vs 19 [72%]; P=0.67).	**Other comments:** As a case series, this study does not have a comparator. 6/46 patients were treated with a different anti-TNF, but results are not available separately for those who had IFX. Selection bias may be present due to the voluntary nature of inclusion in the STAT database. Authors also mention that ePOST is of unknown reproducibility for skin lesions. **Source of funding:** The study is supported by both public and private research grants; the private grants are from Abbvie, Pfizer, Janssen, and MSD and are managed by the French Society of Dermatology, which is one of the sponsors.

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	Cutaneous ePOST, median (range): 5 (1-6)		Infections: 2/21 (9.5%) vs 12/25 (48%; (P=0.02). **SAE**[1] Infections AE: n=14[8] (30%) • UTI (n=6) • bronchopneumonitis (n=7) • sinusitis (n=2) • dental abscess (n=1) • cellulitis (n=1) • angiocholitis (n=1) • herpes zoster (n=1) • flu (n=1) • gastroenteritis (n=1) Hospitalised for infection (grade 3/4): n=7 • pneumonitis (n=3) • UTI (n=1) • herpes zoster (n=1) • facial cellulitis (n=1) • angiocholitis (n=1) **AE leading to discontinuation** N=11 (24%)	
Sakkat A, Cox G, Khalidi N, Larche M, Beattie K, Renzoni EA, et al. Infliximab therapy in refractory sarcoidosis: a multicenter real-world analysis. Respir Res. 2022;23(1):54. **Study location**	**Inclusion criteria** Patients who were prescribed IFX for the treatment of sarcoidosis. IFX was initiated in patients who failed first and second line immunomodulators as determined by a multidisciplinary team of Respirologists,	**Interventions** IFX Induction regimen: 3–5 mg/kg dose at 0, 2 and 6 weeks. Then every 4–8 weeks, with total duration individualized based on clinical response, adverse events, and the availability of payee funding.	**Critical outcomes** **Mortality** N=1 (progressive respiratory failure, not considered a complication of IFX) **Steroid use reduction** (data for 22 patients on IFX)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. No information 5. No information

Study details	Population	Intervention	Study outcomes	Appraisal and funding
Databases from 3 tertiary referral centres in Canada (n=1) and UK (n=2) **Study type** Case series **Study aim** To investigate the long-term effectiveness of IFX in an international multi-centre retrospective cohort of patients with refractory sarcoidosis. **Study dates** February 2009 to May 2019	Dermatologists, ENT specialists, Rheumatologists, and Neurologists at the participating sites. **Exclusion Criteria** Patients with latent tuberculosis (TB) were excluded from treatment using a TB skin test or interferon-gamma release assay. **Total sample size** N=33 **Baseline characteristics** Age 51.6 (range 33-80) Male: 10 (30%) Race: • White 20 (61%) • Black 11 (33%) • Other 2 (6%) $FVC\%_{pred}$: 83.4±28 (range 44.8-135.6) $FEV1\%_{pred}$: 73.5±28.6 (range 23.0-121.8) $DLCO\%_{pred}$: 57.7±24.9 (range 24.0-99.7) Organ for which IFX initiated, n (%): • Lungs: 14 (33) • Skin: 12 (28)	Concomitant therapy, n (%) Corticosteroid alone: 5 (15) 2^{nd} line immunosuppressive alone: 9 (27) Corticosteroid + 2^{nd} line immunosuppressive: 19 (58) **Comparators** No comparator. **Follow-up** Varied depending on physician practice and organ for which IFX initiated. 12 months for FEV1	Baseline: 21.7±12.7 mg/day End of follow-up: 10.5±8.3 mg/day **Important outcomes** **Sarcoid disease activity** Relapse following treatment discontinuation due to improvement or resolution of disease activity: 7/11 patients (63.6%), median time to relapse 8±2.04 months 10/16 index organs (62.5%), median time to relapse and 8±2.55 months **Organ-specific disease activity** **Pulmonary function** **12 months** Increase in FEV1: +90 ml (55%) (95% CI −0.31 to 0.39) Change in FVC: −20 ml (−0.77%) (95% CI −0.18 to 0.24) **Organ-specific treatment success** % (95% CI) with treatment success, **follow-up unclear (up to 12 months assumed)** **Pulmonary function (n=14)** Treatment success = increase in absolute FVC or FEV1 by > 10% or No change in FVC or FEV1 (± 10% from baseline): 78.6% (49.2 to 95.3)	6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:** As a case series, this study does not have a comparator. 6/33 people had CNS involvement. Other than organ-specific disease activity, outcomes are presented for the whole cohort so include people who do not meet the PICO for this review. **Source of funding:** Unfunded

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	• Upper airway: 7 (16) • CNS: 6 (14) • Peripheral lymph node: 1 (2) • GI: 1 (2) • Uveitis: 1 (2) • Arthritis: 1 (2)		**Cutaneous (n=12)** Treatment success = 50% improvement in skin lesions in comparison to baseline images: 91.7% (61.5 to 99.8) **Upper airway (n=7)** Treatment success = improvement in structural change on serial exam and imaging: 71.5% (29.0 to 96.3) **Peripheral lymph nodes (n=1)** Treatment success = resolution of lymphadenopathy, clinical assessment: 100% (2.5 to 100) **Gastrointestinal (n=1)** Treatment success = resolution of symptoms and normalization of laboratory testing: 100% (2.5 to 100) **Uveitis (n=1)** Treatment success = resolution of symptoms and improvement of abnormalities on serial eye exam: 100% (2.5 to 100) **Arthritis (n=1)** Treatment success = resolution of symptoms and normalization of laboratory testing: 100% (2.5 to 100) **SAE** Adverse events[1], n (%) • None 8 (24) • Pneumonia 6 (18) • Leukopenia 5 (15) • Infusion reaction 4 (12)	

Study details	Population	Intervention	Study outcomes	Appraisal and funding
			• Minor infection (1 each of cellulitis, cholecystitis, and recurrent sinusitis) 3 (9) • Paraesthesias 2 (6) • Anaphylaxis 4 (12) • Flare of cutaneous disease 1 (3) • Chest pain 1 (3) • Headache 1 (3) • Asthma 1 (3) **AE leading to discontinuation** 7/33 patients (21%): • recurrent infusion reactions associated with pruritus and paraesthesias (n=2) • anaphylaxis (n=4, 3 of which occurred following a period of treatment interruption) • acute flare of lupus pernio following first IFX infusion (n=1)	
Van Rijswijk HNAJ, Vorselaars ADM, Ruven HJT, Keijsers RGM, Zanen P, Korenromp IHE, et al. Changes in disease activity, lung function and quality of life in patients with refractory sarcoidosis after anti-TNF treatment. Expert Opinion on Orphan Drugs. 2013;1(6):437-43. **Study location** Nieuwegein, The Netherlands **Study type**	**Inclusion criteria** • Refractory to regular medication (corticosteroids, antimalarial drugs, methotrexate) or had severe side effects on this medication. • Unremitting disease activity, objectified by elevated serum markers or increased uptake on PET-scan **Exclusion Criteria** Active or latent tuberculosis infection	**Interventions** IFX (IV) at dose of 5 mg/kg at weeks 0, 2, 6, 10, 14 and 18. Concomitant medication • Methotrexate 16 (35.6) • Prednisone 16 (35.6) • Prednisone and methotrexate 8 (17.8) • Plaquenil 1 (2.2) • None 3 (6.7) • Unknown 1 (2.2) **Comparators** No comparator.	**Critical outcomes** **Mortality** • Not reported, appears to be 0 **HRQL** Baseline (n=27) • Fatigue severity: 49.4±9.2 • Physical functioning: 30.9±22.2 Change from baseline (n=45) • Fatigue severity -5.3±8.5; P= 0.003 • Physical functioning +12.6±23.9; P= 0.011	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. No information 5. No information 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes

Study details	Population	Intervention	Study outcomes	Appraisal and funding
Case series **Study aim** To evaluate change in disease activity and quality of life upon IFX treatment in patients with refractory sarcoidosis. **Study dates** 2004-2010	**Total sample size** N=48 (n=45 analysed) **Baseline characteristics** Age: 48.9±10.1 Male: 27 (60) Scadding stage, n (%) • Stage 0 5 (11.1) • Stage I 7 (15.6) • Stage II 14 (31.1) • Stage III 5 (11.1) • Stage IV 14 (31.1) Pulmonary indication: n=23 (severe cough n=2; sever dyspnoea n=21) Extrapulmonary: n=22 (uveitis n=4, cardiac n=2, neurosarcoidosis and SFN n=9, extreme fatigue n=7)	**Follow-up** 18 weeks	**Steroid use reduction** *"The background medication regimen remained stable during the treatment period as clinical evaluation did not give rise to tempering the initial doses."* **Important outcomes** **Organ-specific disease activity** **Pulmonary function** Baseline pulmonary function tests • VC, % predicted 85.7±19.0 • FEV_1, % predicted 75.3±22.9 • DLCOc, % predicted 66.7±18.7 Change from baseline • VC, % predicted +5.4±7.6; P < 0.0001 • FEV1, % predicted +5.3±8.3; P < 0.001 • DLCOc, % predicted +3.1±7.3; P= 0.012 **Radiographic changes ^{18}F-FDG PET (SUV_{max})** Baseline n=40 • Pulmonary parenchyma 4.3±3.6 • Mediastinum 5.1±3.9 Change from baseline (n=45) • Pulmonary parenchyma -2.7±3.4 (P<0.00005) • Mediastinum -2.3±3.4 (P<0.0005)	**Other comments:** As a case series, this study does not have a comparator. 9/48 patients had neurosarcoidosis and SFN, so do not meet the PICO. Data are not available separately for those patients who meet the PICO. 8 patients (17.8%) had methotrexate treatment at the same time as IFX. Authors state that reanalysis without these patients did not affect the %predicted VC and %predicted FEV1, whereas the impact on DLCOc was no longer significant. Analysis excluded three patients who did not complete all six infusions. **Source of funding:** No statement

Study details	Population	Intervention	Study outcomes	Appraisal and funding
			Normalisation of ACE/cytokines Baseline serum parameters • Serum ACE Z-score: 2.6±3.9 • Serum sIL-2R (pg/ml): 5001±3919 Change from baseline • Serum ACE Z-score: -2.01±3.31; P < 0.0005 • Serum sIL-2R (pg/ml): -2879±3755; P<0.00001 **SAE** • Hospitalisation due to pneumonia (n=1) • Tuberculosis (n=0) **AE leading to discontinuation** Severe infusion reaction (n=1)	
Vorselaars AD, Crommelin HA, Deneer VH, Meek B, Claessen AM, Keijsers RG, et al. Effectiveness of infliximab in refractory FDG PET-positive sarcoidosis. Eur Respir J. 2015;46(1):175-85. **Study location** Nieuwegein, The Netherlands **Study type** Case series	**Inclusion criteria** Severe sarcoidosis, unresponsive to first- and second-line treatment, or severe side-effects from these agents **Exclusion Criteria** Vaccination in previous 3 months, active or untreated latent TB, serious infections in last 2 months, serious right ventricular heart failure, active hepatitis, history of allergic reactions to monoclonal antibodies or	**Interventions** IFX intravenously following a standard protocol starting with 5 mg/kg^{-1} bodyweight at weeks 0 and 2 and then every 4 weeks over a period of 6 months. Dosing of prednisone could be tapered according to the judgement of the treating physician. **Comparators** No comparator.	**Critical outcomes** **Mortality** N=1 during study N=1 several months after treatment discontinuation **HRQL, mean PGA score (VAS)** Baseline 61.0 out of 100 Change at 26 weeks −14.6 (P<0.0001) (clinical improvement)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes

Study details	Population	Intervention	Study outcomes	Appraisal and funding
Study aim To study the effect of IFX in a prospective clinical setting, and to investigate whether sarcoidosis phenotype, inflammatory activity, IFX trough levels or formation of antibodies against IFX are related to the initial response rate after 26 weeks. **Study dates** January 2011 - April 2013	their fragments, opportunistic infections within the last 6 months, HIV, transplantation, known malignancy, pregnancy or breastfeeding **Total sample size** N = 56 **Baseline characteristics** Age (years) 48.7±10.1 Male 36/56 (64.3%) Caucasian: 49 (87.5) • Disease duration (years) 6.8±7.1 Main treatment indication: • Pulmonary 34 (60.7) • Cardiac 2 (3.6) • Small fibre neuropathy 8 (14.3) • Cutaneous 4 (7.2) • Central nervous system 3 (5.4) • Other 5 (9.0) Measures of disease activity/severity • SUV_{max} total (including index localisation) 9.0±5.2 • ACE $U \cdot L^{-1}$ 89.73±49.7 • ACE Z-score 4.26±4.8	**Follow-up** 6 months	**HRQL, SF-36 (physical functioning)** Baseline 40.6 out of 100 Change at 6 months + 8.2 (P=0.009) (improvement) **Steroid use reduction** Baseline 19/56 used prednisone at start of study; mean dose not reported 6 months, change in mean dose -8.8 mg (P=0.001). **Important outcomes** **Sarcoid disease activity** Composite overall response (organ function, inflammatory activity, QoL) • excellent response: 40% • good response: 39% • partial response: 17% • no response: 4% % with response for each component of composite • Organ function: 69% • Inflammation: 79% • QoL: 67% **Organ-specific disease activity**	10. Yes **Other comments:** Paper describes this as a prospective, open-label trial. This has been classified as a case series for the purposes of this review as there is no comparator treatment. 11/56 had CNS/SFN involvement, so do not meet the PICO for this review. Outcome data include these patients as well as those in scope. Authors mention a limitation of their composite response score is that deterioration in one category is not taken into account when another category is improving. **Source of funding:** Study was supported by a research grant from the St Antonius Hospital innovation fund.

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	• sIL-2R pg·mL^{-1} 8824±8503 Scadding Radiographic Stage 0: 5 (8.9%) I: 6 (10.7%) II: 16 (28.6%) III: 14 (25.0%) IV: 15 (26.8%)		**Pulmonary function (for subgroup with pulmonary disease, n=28)** Baseline • FVC% pred: 73.6 • FEV1% pred: 55.8 • DLCOC % pred: 56.6 • 6MWD % pred: 61.0 Change at 6 months • FVC% pred: +6.6 (P=0.0007) • FEV1% pred: +5.8 (P<0.0001) • DLCOC % pred: +4.1 (P=0.001) • 6MWD % pred: +4.2 (P value not reported) **Radiographic changes, mean±SD** For mixed sarcoidosis group (n=56) Baseline SUVmax lung parenchyma 6.6±5.3 SUVmax mediastinum 5.7±3.2 SUVmax total (including index localisation) 9.0±5.2 Change at 6 months (n=49) SUV_{max} lung parenchyma: -3.93 (P<0.0001) SUV_{max} mediastinum: -2.97 (P<0.0001) SUV_{max} lungs and index localisation (e.g. heart): -5.76 (P<0.0001) For subgroup with pulmonary sarcoidosis (n=28) Baseline	

Study details	Population	Intervention	Study outcomes	Appraisal and funding
			SUV_{max} lung parenchyma: 9.0±5.0 SUV_{max} mediastinum: 5.9±3.3 SUV_{max} index localisation: 9.8±5.3 Change at 6 months SUV_{max} lung parenchyma: -5.3±5.6 SUV_{max} mediastinum: -2.7±3.8 SUV_{max} index localisation: -5.5±5.6 **Normalisation of ACE/cytokines, mean±SD** Main mixed sarcoidosis group (n=56) Baseline ACE U/L 89.73±49.7 ACE Z-score 4.26±4.8 sIL-2R pg/mL 8824±8503 Change at 6 months (n=49 for ACE, n=47 for sIL-2R) ACE U/L -28.2 U/L (P=0.0003) ACE Z-score not reported sIL-2R pg/ml -4269.4 (P<0.0001). Pulmonary indication subgroup (n=28) Baseline ACE U/L: 86.2±46 ACE Z score: 3.7±3.9 SIL-2R pg/mL: 7631±4259 Change at 6 months ACE U/L: -21.8±43.3 ACE Z score: -1.78±3.33 SIL-2R pg/mL: -3955±3883	

Study details	Population	Intervention	Study outcomes	Appraisal and funding
			SAE Pneumonia, requiring hospitalisation and discontinuation of therapy n = 3 **AE leading to discontinuation** Hospitalised with severe progressive disease and discontinued (n=1) Peritonitis (n=1 with peritoneal dialysis at baseline) Severe gastrointestinal complaints (n=1) Allergic reactions (n=2, 1 discontinued) Discontinued for undisclosed symptoms (n=1)	

Abbreviations

ACE: angiotensin-converting enzyme; AE: adverse events; CIS: Checklist Individual Strength; CNS: central nervous system; DLCO: diffusing capacity of the lungs for carbon monoxide; DLCOc diffusing capacity for carbon monoxide corrected for haemoglobin; ECG: electrocardiography; EF: ejection fraction; ePOST: extrapulmonary Physician Organ Severity Tool; FEV1: forced expiratory volume in 1 second; ^{18}F-FDG PET (SUVmax): maximum standard uptake value on positron emission tomography (PET) using glucose analogue fluorine-18-labeled fluorodeoxyglucose (FDG); FVC: forced vital capacity; HRQL: Health-related quality of life; ICD: implantable cardioverter defibrillator; IFX: infliximab; IS: immunosuppressive agents; IV: intravenous; JBI: Joanna Briggs Institute; LVEF: left ventricular ejection fraction; OCRR: overall cutaneous response rate; PB: placebo; PET: positron emission tomography; PGA: Patient Global Assessment; Pred: predicted; QoL: quality of life; RCT: randomised controlled trial; ROB: risk of bias SAE: serious adverse events; SD: standard deviation; SFN: small fibre neuropathy; SF-36: 36-item Short Form questionnaire; sIL-2R: soluble interleukin-2 receptor; STAT: Sarcoidosis Treated with Anti-TNF; SUVmax: maximum standard uptake value; TB: tuberculosis; UTI: urinary tract infection; VC: vital capacity; WASOG: World Association for Sarcoidosis and Other Granulomatous Disorders; 6MWD: six-minute walking distance

[1]SAE not reported separately from AE

Appendix F Quality appraisal checklists

Cochrane RoB 1 tool for RCTs

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other bias

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Infliximab	Placebo	Result		
Mortality (1 RCT, 6 case-series)									
Mortality at 6 weeks, pulmonary sarcoidosis									
1 RCT Rossman et al 2006	Very serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[2]	13	6	IFX vs PB: 1/13 vs 0/6	Critical	Very low
Mortality at 18 weeks, mixed sarcoidosis									
1 case series Van Rijswijk et al 2013	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	N=0	Critical	Very low
Mortality at 6 months, mixed sarcoidosis									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	56	None	N=1 during study *N=1 several months after treatment discontinuation*	Critical	Very low
Mortality at 12 months, cardiac sarcoidosis									
1 case series Gilotra et al 2021	No serious limitations	Very serious indirectness[5]	Not applicable	Not calculable	38 (30 on infliximab)	None	N=0	Critical	Very low
Mortality at 12 months, cardiac sarcoidosis									
1 case series Harper et al 2019	No serious limitations	Serious indirectness[6]	Not applicable	Not calculable	36	None	N=0	Critical	Very low
Mortality at 12 months, cutaneous sarcoidosis									
1 case series Heidelberger et al 2017	No serious limitations	Very serious indirectness[7]	Not applicable	Not calculable	46	None	N=1[8]	Critical	Very low
Mortality, follow-up varied (up to 12 months), mixed sarcoidosis									
1 case series	No serious limitations	Very serious indirectness[9]	Not applicable	Not calculable	33	None	N=1	Critical	Very low

Sakkat et al 2022									
HRQL (1 RCT, 2 case-series)									
HRQL at 6 weeks, pulmonary sarcoidosis (SF-36: 0-100 scale, lower scores indicate lower HRQL)									
1 RCT Rossman et al 2006	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	13	6	SF-36 (baseline) IFX vs PB: 26.72±0.45 vs 26.43±0.83 SF-36 (week 6) IFX vs PB: 27.11±0.46 vs 26.4±0.81	Critical	Low
HRQL at 18 weeks, mixed sarcoidosis (fatigue severity (CIS: higher scores indicate greater fatigue): and physical functioning (SF-36): 0-100 scale, lower scores indicate lower HRQL). Change from baseline, mean±SD									
1 case series Van Rijswijk et al 2013	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	Fatigue severity -5.3±8.5; P=0.003 Physical functioning +12.6±23.9; P=0.011	Critical	Very low
HRQL at 6 months, mixed sarcoidosis (PGA 0-100 scale, higher scores indicate lower HRQL, and physical functioning (SF-36): 0-100 scale, lower scores indicate lower QoL). Change from baseline, mean									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	56	None	PGA: −14.6 (P<0.0001) SF-36 (physical functioning): +8.2 (P=0.009)	Critical	Very low
Steroid use reduction (6 case series)									
Steroid use reduction at 18 weeks, mixed sarcoidosis									
1 case series Van Rijswijk et al 2013	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	No dose reduction	Critical	Very low
Steroid use reduction (mg/day) at 6 months, mixed sarcoidosis									
Steroid use at 6 months, cardiac sarcoidosis, mean±SD dose									
1 case series Gilotra et al 2021	No serious limitations	Very serious indirectness[5]	Not applicable	Not calculable	38 (30 on infliximab)	None	Baseline: 21.7±17.5mg/d 6 months: 10.4±6.1mg/d (P=0.001)	Critical	Very low
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	56 (n=19 on prednisone at baseline)	None	Mean daily dose change: -8.8mg/d (P=0.001)	Critical	Very low

Steroid use at 12 months, cardiac sarcoidosis, mean±SD dose									
1 case series Gilotra et al 2021	No serious limitations	Very serious indirectness[5]	Not applicable	Not calculable	38 (30 on infliximab)	None	Baseline: 21.7±17.5mg/d 12 months: 7.3±7.3 mg/d (P=0.002)	Critical	Very low
Steroid dose (mg/day), median (25th -75th) at 6 months, cardiac sarcoidosis									
1 case series Harper et al 2019	No serious limitations	Serious indirectness[6]	Not applicable	Not calculable	36	None	Baseline: 20 (10 to 30) (n=35) 6 months: 7.5 (2.5 to 15) (n=35) P<0.01 for reduction	Critical	Very low
Steroid dose (mg/day), median (25th -75th) at 12 months, cardiac sarcoidosis									
1 case series Harper et al 2019	No serious limitations	Serious indirectness[6]	Not applicable	Not calculable	36	None	Baseline: 20 (10 to 30) (n=35) 12 months: 5 (0 to 10) (n=29) P<0.01 for reduction	Critical	Very low
Steroid use (mean dose) at up to 12 months, cutaneous sarcoidosis									
1 case series Heidelberger et al 2017	No serious limitations	Very serious indirectness[7]	Not applicable	Not calculable	46	None	Baseline: 17.5 mg/d Last follow-up: 8.4 mg/d (P<0.001)	Critical	Very low
Steroid use (mean dose, mg/d), follow-up varied (up to 12 months), mixed sarcoidosis									
1 case series Sakkat et al 2022	No serious limitations	Very serious indirectness[9]	Not applicable	Not calculable	22/33	None	Baseline: 21.7±12.7 End of follow-up: 10.5±8.3	Critical	Very low
Sarcoid disease activity (4 case-series)									
Composite overall response, mixed sarcoidosis, change from baseline to 6 months									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	56	None	Composite overall response (organ function, inflammatory activity, QoL) • excellent response: 40% • good response: 39% • partial response: 17% • no response: 4%	Important	Very low
Sarcoid disease activity at 12 months, cardiac sarcoidosis									
1 case series Harper et al 2019	No serious limitations	Serious indirectness[6]	Not applicable	Not calculable	36	None	Responder: 24/36 (20 had steroid dose reduction; 12 had improved dysrhythmia control; EF improved in 8)	Important	Very low

							Non-responder: 9/36 (although 5 had improvement in at least 1 domain; 2 received heart transplants) Stable: 3/36		
Sarcoid disease activity at 12 months, cutaneous sarcoidosis									
1 case series Heidelberger et al 2017	No serious limitations	Very serious indirectness[7]	Not applicable	Not calculable	46	None	Responders: 31/46 (13 complete, 18 partial) 11/31 responders relapsed	Important	Very low
Sarcoid disease activity, follow-up varied (up to 12 months), mixed sarcoidosis									
1 case series Sakkat et al 2022	No serious limitations	Very serious indirectness[9]	Not applicable	Not calculable	11/33	None	Relapse following treatment discontinuation (due to improvement or resolution of disease activity): 7/11 patients (63.6%) Median time to relapse 8±2.04 months	Important	Very low
Organ-specific disease activity (1 RCT, 6 case-series)									
Pulmonary function at 6 weeks, pulmonary sarcoidosis, vital capacity (higher values indicate better pulmonary function)									
1 RCT Rossman et al 2006	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	13	6	Per cent change in expected vital capacity (baseline to week 6) IFX vs PB: 15.22±9.91% vs 8.39±3.33% VC_{obs} (baseline) IFX vs PB: 2.47±0.2 vs 2.37±0.31 VC_{obs} (6 weeks) IFX vs PB: 2.65±0.19 vs 2.40±0.28 $VC\%_{exp}$ (baseline) IFX vs PB: 59.63±3.69 vs 65.5±2.99 $VC\%_{exp}$ (6 weeks) IFX vs PB: 64.68±3.60 vs 67.67±3.31	Important	Low

							15% improvement in VC (6 weeks) IFX vs PB: 2/13 vs 0/6		
Pulmonary function, mixed sarcoidosis, vital capacity % predicted (higher values indicate better pulmonary function), change from baseline to 18 weeks									
1 case series Van Rijswijk et al 2013	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	+5.4±7.6; P<0.0001	Important	Very low
Pulmonary function, mixed sarcoidosis, FEV1 % predicted (higher values indicate better pulmonary function), change from baseline to 18 weeks									
1 case series Van Rijswijk et al 2013	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	+5.3±8.3; P<0.001	Important	Very low
Pulmonary function, mixed sarcoidosis, DLCOc, % predicted (higher values indicate better pulmonary function), change from baseline to 18 weeks									
1 case series Van Rijswijk et al 2013	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	DLCOc, % predicted +3.1±7.3; P=0.012	Important	Very low
Pulmonary function, mixed sarcoidosis with pulmonary treatment indication, FVC% predicted (higher values indicate better pulmonary function), change from baseline to 6 months,									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	28	None	+6.6 (P=0.0007)	Important	Very low
Pulmonary function, mixed sarcoidosis with pulmonary treatment indication, FEV1% predicted (higher values indicate better pulmonary function), change from baseline to 6 months									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	28	None	+5.8 (P<0.0001)	Important	Very low
Pulmonary function, mixed sarcoidosis with pulmonary treatment indication, DLCO% predicted (higher values indicate better pulmonary function), change from baseline to 6 months									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	28	None	+4.1 (P=0.001)	Important	Very low
Pulmonary function, mixed sarcoidosis with pulmonary treatment indication, 6MWD% predicted (higher values indicate better pulmonary function), change from baseline to 6 months									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	28	None	+4.2 (P not reported)	Important	Very low

Pulmonary function, mixed sarcoidosis, FEV1 (ml (% change) (95% CI) (higher values indicate better pulmonary function), **change from baseline to 12 months**									
1 case series Sakkat et al 2022	No serious limitations	Serious indirectness[10]	Not applicable	Not calculable	14	None	+ 90 ml (+55%) (95% CI −0.31 to 0.39)[11] Change in FVC −20 ml (−0.77%) (95% CI −0.18 to 0.24)	Important	Very low
Pulmonary function, mixed sarcoidosis, FVC (ml (% change) (95% CI) (higher values indicate better pulmonary function), **change from baseline to 12 months**									
1 case series Sakkat et al 2022	No serious limitations	Serious indirectness[10]	Not applicable	Not calculable	14	None	− 20 ml (−0.77%) (95% CI −0.18 to 0.24)	Important	Very low
Organ-specific disease activity, % (95% CI) with treatment success for pulmonary function = increase in absolute FVC or FEV1 by >10% or no change in FVC or FEV1 (± 10% from baseline). Time point unclear, assumed to be 12 months.									
1 case series Sakkat et al 2022	No serious limitations	Serious indirectness[10]	Not applicable	Not calculable	14	None	78.6% (49.2 to 95.3)	Important	Very low
Organ-specific disease activity, % (95% CI) with treatment success for upper airway = improvement in structural change on serial exam and imaging. Time point unclear, assumed to be 12 months.									
1 case series Sakkat et al 2022	No serious limitations	Serious indirectness[10]	Not applicable	Not calculable	7	None	71.5% (29.0 to 96.3)	Important	Very low
Cardiac function (LVEF %, mean±SD) (higher values indicate better cardiac function), at 6 months, cardiac sarcoidosis									
1 case series Gilotra et al 2021	No serious limitations	Very serious indirectness[5]	Not applicable	Not calculable	38 (30 on infliximab)	None	Baseline: 52.6±15.9 (n=37) 6 months: 53.8±17.1 (n=26)	Important	Very low
Cardiac function (LVEF %, mean±SD) (higher values indicate better cardiac function), at 12 months, cardiac sarcoidosis									
1 case series Gilotra et al 2021	No serious limitations	Very serious indirectness[5]	Not applicable	Not calculable	38 (30 on infliximab)	None	Baseline: 52.6±15.9 (n=37) 12 months: 49.3±16.1 (n=15)	Important	Very low
Cardiac function (EF (%) (higher values indicate better cardiac function), median (25^{th} -75^{th})) at 6 months, cardiac sarcoidosis									
1 case series Harper et al 2019	No serious limitations	Very serious indirectness[6]	Not applicable	Not calculable	36	None	Baseline: 41 (32 to 55) (n=31) 6 months: 41 (35 to 54) (n=28) P=0.43 for change	Important	Very low
Cardiac function (ICD therapy, n (%)) (lower values indicate better cardiac function), at 6 months, cardiac sarcoidosis									
1 case series	No serious limitations	Very serious indirectness[6]	Not applicable	Not calculable	36	None	Baseline: 4 (16) (n=25) 6 months: 2 (8.7) (n=23)	Important	Very low

Harper et al 2019									
Cardiac function (ICD therapy, n (%)) (lower values indicate better cardiac function), at 12 months, cardiac sarcoidosis									
1 case series Harper et al 2019	No serious limitations	Very serious indirectness[6]	Not applicable	Not calculable	36	None	Baseline: 4 (16) (n=25) 12 months: 2 (12.5) (n=16) P=0.45 for change	Important	Very low
Overall cutaneous response rate at 3 months, % (95% CI) cutaneous sarcoidosis									
1 case series Heidelberger et al 2017	No serious limitations	Very serious indirectness[7]	Not applicable	Not calculable	46	None	24% (95% CI 14% to 40%)	Important	Very low
Overall cutaneous response rate at 6 months, % (95% CI) cutaneous sarcoidosis									
1 case series Heidelberger et al 2017	No serious limitations	Very serious indirectness[6]	Not applicable	Not calculable	46	None	46% (95% CI 32% to 62%)	Important	Very low
Overall cutaneous response rate at 12 months, % (95% CI) cutaneous sarcoidosis									
1 case series Heidelberger et al 2017	No serious limitations	Very serious indirectness[7]	Not applicable	Not calculable	46	None	79% (95% CI 64% to 98%)	Important	Very low
Median ePOST severity score at up to 12 months, % (95% CI) cutaneous sarcoidosis (ePOST scores: 0 (not affected) to 6 (very severe involvement))									
1 case series Heidelberger et al 2017	No serious limitations	Very serious indirectness[7]	Not applicable	Not calculable	46	None	Baseline: 5 Last follow-up: 3		Very low
Organ-specific disease activity, % (95% CI) with treatment success for cutaneous sarcoidosis =50% improvement in skin lesions in comparison to baseline images. Time point unclear, assumed to be 12 months.									
1 case series Sakkat et al 2022	No serious limitations	Serious indirectness[10]	Not applicable	Not calculable	12	None	91.7% (61.5 to 99.8)	Important	Very low
Organ-specific disease activity, % (95% CI) with treatment success for peripheral lymph nodes = resolution of lymphadenopathy, clinical assessment. Time point unclear, assumed to be 12 months.									
1 case series Sakkat et al 2022	No serious limitations	Serious indirectness[10]	Not applicable	Not calculable	1	None	100% (2.5 to 100)	Important	Very low
Organ-specific disease activity, % (95% CI) with treatment success for gastrointestinal sarcoidosis = resolution of symptoms and normalization of laboratory testing. Time point unclear, assumed to be 12 months.									
1 case series Sakkat et al 2022	No serious limitations	Serious indirectness[10]	Not applicable	Not calculable	1	None	100% (2.5 to 100)	Important	Very low

Organ-specific disease activity, % (95% CI) with treatment success for uveitis = resolution of symptoms and improvement of abnormalities on serial eye exam. Time point unclear, assumed to be 12 months.									
1 case series Sakkat et al 2022	No serious limitations	Serious indirectness[10]	Not applicable	Not calculable	1	None	100% (2.5 to 100)	Important	Very low
Organ-specific disease activity, % (95% CI) with treatment success for arthritis = resolution of symptoms and normalization of laboratory testing. Time point unclear, assumed to be 12 months.									
1 case series Sakkat et al 2022	No serious limitations	Serious indirectness[10]	Not applicable	Not calculable	1	None	100% (2.5 to 100)	Important	Very low
Radiographic changes (1 RCT, 3 case series). Lower ^{18}F-FDG PET (SUVmax) scores indicate less disease activity									
Radiologic improvement at 6 weeks, pulmonary sarcoidosis									
1 RCT Rossman et al 2006	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	13	6	IFX vs PB: 23.0% vs 0%	Important	Low
^{18}F-FDG PET (SUVmax mean±SD), mixed sarcoidosis, change from baseline to 18 weeks									
1 case series Van Rijswijk et al 2013	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	Pulmonary parenchyma -2.7±3.4 (P<0.00005) Mediastinum -2.3±3.4 (P<0.0005)	Important	Very low
Radiographic changes (SUVmax mean±SD) at 6 months, cardiac sarcoidosis									
1 case series Gilotra et al 2021	No serious limitations	Very serious indirectness[5]	Not applicable	Not calculable	38 (30 on infliximab)	None	Baseline: 4.1±4.5 (n=34) 6 months: 0.54±1.6 (n=23)	Important	Very low
Radiographic changes (SUVmax mean±SD) at 12 months, cardiac sarcoidosis									
1 case series Gilotra et al 2021	No serious limitations	Very serious indirectness[5]	Not applicable	Not calculable	38 (30 on infliximab)	None	Baseline: 4.1±4.5 (n=34) 12 months: 0.65±1.5 (n=11)	Important	Very low
Radiographic changes, mixed sarcoidosis with pulmonary treatment indication, (SUVmax mean±SD) change from baseline to 6 months, mean±SD									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	28	None	Lung parenchyma: -5.3±5.6 Mediastinum: -2.7±3.8 Index localisation: -5.5±5.6	Important	Very low
Radiographic changes, mixed sarcoidosis, (SUVmax mean±SD) change from baseline to 6 months, mean±SD									
1 case series	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	56	None	Lung parenchyma: -3.93 (p<0.0001)	Important	Very low

Vorselaars et al 2015							Mediastinum: -2.97 (P<0.0001) Lungs and index localisation (e.g. heart): -5.76 (P<0.0001)		
Normalisation of ACE/cytokines (2 case series) (reductions or lower scores indicate less disease activity)									
ACE Z-score, mixed sarcoidosis, change from baseline to 18 weeks									
1 case series Van Rijswijk et al 2013	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	Serum ACE Z-score: -2.01±3.31; P<0.0005	Important	Very low
Serum sIL-2R (pg/ml), mixed sarcoidosis, change from baseline to 18 weeks									
1 case series van Rijswijk 2013	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	Serum sIL-2R (pg/ml): -2879±3755; P<0.00001	Important	Very low
ACE U/L, mixed sarcoidosis with pulmonary treatment indication, change from baseline to 6 months									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	28	None	-21.8±43.3	Important	Very low
ACE Z-score, mixed sarcoidosis with pulmonary treatment indication, change from baseline to 6 months									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	28	None	-1.78±3.33	Important	Very low
Serum sIL-2R (pg/ml), mixed sarcoidosis with pulmonary treatment indication, change from baseline to 6 months									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	28	None	-3955±3883	Important	Very low
ACE U/L, mixed sarcoidosis, change from baseline to 6 months									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	49	None	-28.2 (P=0.0003)	Important	Very low
Serum sIL-2R (pg/ml), mixed sarcoidosis, change from baseline to 6 months									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	47	None	4269.4 (P<0.0001)	Important	Very low

Serious adverse events (1 RCT, 6 case series)									
AE at 6 weeks, pulmonary sarcoidosis									
1 RCT Rossman et al 2006	Very serious limitations[1]	No serious indirectness	Not applicable	No serious imprecision	13	6	IFX vs PB: 1 or more AE: 2/13 vs 1/6 right leg cellulitis; acute renal failure, pulmonary emboli, cellulitis (all 3): 1/13 vs 0/6 decreased white blood cell count and elevated creatine phosphokinase: 1/13 vs 0/6 Severe shortness of breath: 0/13 vs 1/6	Important	Low
SAE at 18 weeks, mixed sarcoidosis									
1 case series Van Rijswijk et al 2013	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	Hospitalisation due to pneumonia (n=1) Tuberculosis (n=0)	Important	Very low
SAE at 6 months, mixed sarcoidosis									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	56	None	**SAE** Pneumonia, requiring hospitalisation and discontinuation of therapy (n=3)	Important	Very low
SAE at 12 months, cardiac sarcoidosis									
1 case series Gilotra et al 2021	No serious limitations	Very serious indirectness[5]	Not applicable	Not calculable	38 (30 on infliximab)	None	N=5 (3 shingles, 1 metapneumovirus pneumonia, 1 urinary tract infection)	Important	Very low
SAE at 12 months, cardiac sarcoidosis									
1 case series Harper et al 2019	No serious limitations	Very serious indirectness[6]	Not applicable	Not calculable	36	None	N= had adverse events but continued: • Pneumonia pulmonary embolism (n=1) • C. difficile diarrhoea (n=1) • Shingles (n=1) • Sepsis (n=1)	Important	Very low

Serious and non-serious adverse events (not reported separately in this study) at up to 12 months, % (95% CI), cutaneous sarcoidosis									
1 case series Heidelberger et al 2017	No serious limitations	Very serious indirectness[7]	Not applicable	Not calculable	46	None	Infections AE: n=14[8] (30%) • UTI (n=6) • bronchopneumonitis (n=7) • sinusitis (n=2) • dental abscess (n=1) • cellulitis (n=1) • angiocholitis (n=1) • herpes zoster (n=1) • flu (n=1) • gastroenteritis (n=1) Hospitalised for infection (grade 3 or 4): n=7 • pneumonitis (n=3) • UTI (n=1) • herpes zoster (n=1) • facial cellulitis (n=1) • angiocholitis (n=1)	Important	Very low
Serious and non-serious adverse events, n (%) (not reported separately), follow-up varied (up to 12 months), mixed sarcoidosis									
1 case series Sakkat et al 2022	No serious limitations	Very serious indirectness[9]	Not applicable	Not calculable	33	None	• None 8 (24) • Pneumonia 6 (18) • Leukopenia 5 (15) • Infusion reaction 4 (12) • Minor infection (1 each of cellulitis, cholecystitis, and recurrent sinusitis) 3 (9) • Paraesthesias 2 (6) • Anaphylaxis 4 (12) • Flare of cutaneous disease 1 (3) • Chest pain 1 (3) • Headache 1 (3) • Asthma 1 (3)	Important	Very low
Adverse events leading to discontinuation (1 RCT, 6 case series)									
Adverse events leading to discontinuation at 6 weeks, pulmonary sarcoidosis									
1 RCT Rossman et al 2006	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	13	6	Discontinuations (reasons not given) IFX vs PB: 15% vs 17%	Important	Low
Adverse events leading to discontinuation at 18 weeks, mixed sarcoidosis									
1 case series	No serious limitations	Very serious indirectness[3]	Not applicable	Not calculable	45	None	Severe infusion reaction (n=1)	Important	Very low

Van Rijswijk et al 2013									
Adverse events leading to discontinuation at 6 months, mixed sarcoidosis									
1 case series Vorselaars et al 2015	No serious limitations	Very serious indirectness[4]	Not applicable	Not calculable	56	None	Hospitalised with severe progressive disease and discontinued (n=1) Peritonitis (n=1 with peritoneal dialysis at baseline) Severe gastrointestinal complaints (n=1) Allergic reactions (n=2, 1 discontinued) Discontinued for undisclosed symptoms (n=1)	Important	Very low
Adverse events leading to discontinuation at 12 months, cardiac sarcoidosis									
1 case series Gilotra et al 2021	No serious limitations	Very serious indirectness[5]	Not applicable	Not calculable	38 (30 on infliximab)	None	1 intra-abdominal collection presumed to be infectious, required discontinuation of infliximab for 4 months	Important	Very low
Adverse events leading to discontinuation at 12 months, cardiac sarcoidosis									
1 case series Harper et al 2019	No serious limitations	Very serious indirectness[6]	Not applicable	Not calculable	36	None	• Disseminated cryptococcus (n=1) • Decompensation of heart failure (not thought due to IFX therapy) (n=1)	Important	Very low
Adverse events leading to discontinuation at up to 12 months, , cutaneous sarcoidosis									
1 case series Heidelberger et al 2017	No serious limitations	Very serious indirectness[7]	Not applicable	Not calculable	46	None	11 (24%)	Important	Very low
Adverse events leading to discontinuation, follow-up varied (up to 12 months), mixed sarcoidosis									
1 case series Sakkat et al 2022	No serious limitations	Very serious indirectness[9]	Not applicable	Not calculable	33	None	7 (21%) • Recurrent infusion reactions associated with pruritus and paraesthesias (n=2); • Anaphylaxis (n=4) • Acute flare of lupus pernio following first IFX infusion (n=1)	Important	Very low

Abbreviations
ACE: angiotensin-converting enzyme; AE: adverse events; CI: confidence interval; CIS: Checklist Individual Strength; DLCOc diffusing capacity for carbon monoxide corrected for haemoglobin ; EF: ejection fraction; ePOST (extra-pulmonary Physician Organ Severity Tool); FEV1: forced expiratory volume in 1 second; ^{18}F-FDG PET (SUVmax): maximum standard uptake value on positron emission tomography (PET) using glucose analogue fluorine-18-labeled fluorodeoxyglucose (FDG); FVC: forced vital capacity; ICD: implantable cardioverter defibrillator; IFX: infliximab; LVEF: left ventricular ejection fraction; PB: placebo; PGA: Patient Global Assessment; QoL: quality of life; RCT: randomised controlled trial; SAE: serious adverse events; SF-36: 36-item Short Form questionnaire; sIL-2R: soluble interleukin-2 receptor; SUVmax: maximum standard uptake value; UTI: urinary tract infection; VC: vital capacity; 6MWD: six-minute walking distance

Footnotes.
1 Bias: very serious limitations due to 1) unclear randomisation and 2) trial is likely underpowered (closed early due to poor recruitment, 19/42 planned participants recruited).
2 Imprecision: serious imprecision due to 0 events in the placebo arm.
3 Indirectness: very serious limitations due to lack of comparator group and inclusion of 9/48 (19%) people who had neurosarcoidosis and SFN.
4 Indirectness: very serious limitations due to lack of comparator group and inclusion of 11/56 (20%) people who had CNS involvement (n=3) or SFN (n=8).
5 Indirectness: very serious limitations due to lack of comparator group and inclusion of 8/38 (21%) people who had adalimumab not infliximab.
6 Indirectness: very serious limitations due to lack of comparator group and inclusion of 12/36 (33%) people who had neurologic involvement in addition to cardiac involvement.
7 Indirectness: very serious limitations due to lack of comparator group and inclusion of 6/46 (13%) people who had adalimumab or etanercept not infliximab.
8 1 person treated with concomitant prednisone and azathioprine died of pneumonitis. Not clear whether this patient had IFX or another anti-TNF.
8 Some patients had more than one infections AE.
9 Indirectness: very serious limitations due to lack of comparator group and inclusion of 6/33 (14%) people who had CNS involvement.
10 Indirectness: Serious limitations due to lack of comparator group; inclusion of 6/33 (14%) people who had CNS involvement not relevant for this outcome as separate data given.
11 The confidence interval is as presented in the paper, but does not appear to include the difference of 90 ml (+55%) (95% CI − 0.31 to 0.39).

Glossary

Term	Definition
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Adverse reaction	An unintended reaction that is harmful or otherwise unwanted which is experienced by a person after having a drug or any other treatment or intervention, and which is suspected to be related to, or caused by the drug, treatment or intervention
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
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.
Clinical importance or significance	A benefit from treatment that relates to an important outcome such as length of life, and is large enough to be important to patients and health professionals. As an example, it might include a general reduction in symptoms, less pain or improved breathing. Effects identified as statistically significant are not always clinically significant, because the effect is small or the outcome is not important. For example, if a treatment might lower blood pressure but there may be no evidence that this leads to an important clinical outcome, such as a lower risk of stroke or heart attack.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
Confidence interval	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention (sometimes called 'usual care') or a dummy intervention (placebo). The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as

Term	Definition
	possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
Cost effectiveness	Value for money: how well a technology works in relation to how much it costs.
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Follow-up	Observation over a period of time of a person, group or defined population to observe changes in health status, or health- and social care-related variables.
GRADE	GRADE, or grading of recommendations assessment, development and evaluation, is a systematic and explicit approach to grading the quality of evidence and the strength of recommendations.
Health-related quality of life	A combination of a person's physical, mental and social well-being; not merely the absence of disease.
Indication	A symptom or condition needing an intervention.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic test or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet. Examples of social care interventions could include safeguarding or support for carers.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Outcomes	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Depending on the intervention, outcomes could include changes in knowledge and behaviour related to health or in people's health and wellbeing, the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, symptoms or situation.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. However, a statistically significant difference is not necessarily clinically significant. For example, drug A might relieve pain and stiffness statistically significantly more than drug B. But, if the difference in average time taken is only a few minutes, it may not be clinically significant. See Minimal clinically important difference. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
PICO	A PICO (population, intervention, comparison and outcome) framework is a structured approach for developing review questions. It divides each question into 4 components: the population (the population being studied);

Term	Definition
	the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Placebo	A fake (or dummy) treatment given to patients in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to patients in the experimental group). The aim is to determine what effect the experimental treatment has had - over and above any placebo effect caused because someone has had (or thinks they have had) care or attention.
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Randomised controlled trial	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance. See P value.
Subgroup analysis	A way to find out from a study if a treatment is more effective in one group of people (for example, who are a particular age or have particular symptoms) than another. It uses evidence from a defined subgroup within the whole analysis set.

References

Included studies

- 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.
- Harper LJ, McCarthy M, Ribeiro Neto ML, Hachamovitch R, Pearson K, Bonanno B, et al. Infliximab for Refractory Cardiac Sarcoidosis. Am J Cardiol. 2019;124(10):1630-5.
- Heidelberger V, Ingen-Housz-Oro S, Marquet A, Mahevas M, Bessis D, Bouillet L, et al. Efficacy and Tolerance of Anti-Tumor Necrosis Factor alpha Agents in Cutaneous Sarcoidosis: A French Study of 46 Cases. JAMA Dermatol. 2017;153(7):681-5.
- Rossman MD, Newman LS, Baughman RP, Teirstein A, Weinberger SE, Miller W, Jr., et al. A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2006;23(3):201-8.
- Sakkat A, Cox G, Khalidi N, Larche M, Beattie K, Renzoni EA, et al. Infliximab therapy in refractory sarcoidosis: a multicenter real-world analysis. Respir Res. 2022;23(1):54.
- Van Rijswijk HNAJ, Vorselaars ADM, Ruven HJT, Keijsers RGM, Zanen P, Korenromp IHE, et al. Changes in disease activity, lung function and quality of life in patients with refractory sarcoidosis after anti-TNF treatment. Expert Opinion on Orphan Drugs. 2013;1(6):437-43.
- Vorselaars AD, Crommelin HA, Deneer VH, Meek B, Claessen AM, Keijsers RG, et al. Effectiveness of infliximab in refractory FDG PET-positive sarcoidosis. Eur Respir J. 2015;46(1):175-85.

Other references

None

NHS England
Wellington House
133-155 Waterloo Road
London
SE1 8UG