AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: infliximab for the treatment of refractory pulmonary sarcoidosis that has not responded to corticosteroids and other immunosuppressants **(OW23)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
December 2022

Key findings

Licence status
Infliximab is not licensed for treating refractory pulmonary sarcoidosis, where symptoms have not responded to treatment with corticosteroids and at least one other immunosuppressant medicine, such as methotrexate. The use of infliximab in this indication is off-label.

Clinical evidence
The clinical evidence for using infliximab to treat refractory pulmonary sarcoidosis comes from one systematic review, two phase II randomised controlled trials of infliximab (one of which closed early due to lack of enrolment), and observational studies.

Safety
No new safety signals have been observed for infliximab in treating sarcoidosis.

Patient factors
Infliximab is given by intravenous infusion over a 2-hour period. Because of a risk of acute infusion-related reactions, patients should be monitored during the infusion and for at least 2 hours afterwards.

Cost effectiveness
No relevant cost-effectiveness analyses were identified in a literature search.

Budget impact
Clinicians in NHS Wales estimated that 6 people in Wales each year would likely be eligible to receive infliximab to treat refractory pulmonary sarcoidosis. We have assumed that patients would be reviewed after 6 months, and if symptoms improved or stabilised, they would continue for up to two years. This is associated with a cost of [Commercial in confidence figure removed], depending on which brand of infliximab is used. The budget impact is subject to uncertainty.

Impact on health and social care services
In the absence of other licensed medicines, a decision though the One Wales Medicines Process would ensure equity of access to this treatment across Wales.

Innovation and/or advantages
Infliximab offers an additional treatment option for this patient group.

Background

Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment. Infliximab was therefore considered suitable for assessment though the One Wales medicines process.

The All Wales Therapeutics and Toxicology Centre (AWTTC) sought the opinions of clinical experts in Wales, who said that infliximab would be an add-on therapy to the current immunosuppressive routine, as this has shown to reduce the risk of developing infliximab antibodies. They also said that currently there is no comparator medicine. If patients have progressive disease despite standard therapies they would be referred for consideration of lung transplantation or be offered best supportive care.

Access to infliximab for the treatment of refractory pulmonary sarcoidosis is currently by application through the Individual Patient Funding Request (IPFR) process. In the absence of other licensed treatments, a One Wales decision would ensure equity of access to this treatment across the country.

Target group

Patients with refractory pulmonary sarcoidosis that has not responded to treatment with corticosteroids and at least one other immunosuppressive medicine, such as methotrexate.

Marketing authorisation date: Not applicable, off-label

Infliximab is not licensed for the treatment of refractory pulmonary sarcoidosis; its use in this indication is off-label. There are no plans to license infliximab for the indication being considered.

Infliximab is licensed for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriasis arthritis and psoriasis in adults and Crohn's disease in children[1].

Dosing information

The recommended dose is 3 mg/kg or 5 mg/kg, depending upon the indication being treated, given as an intravenous infusion[1], at Weeks 0, 2 and 6, followed by maintenance doses every 8 weeks for 6 months. For pulmonary sarcoidosis the usual starting dose is 3 mg/kg, increased to 5 mg/kg if only a minimal improvement has been seen by the fourth dose[2]. Maintenance treatment might continue for 1 year or 2 years.

Clinical background

Sarcoidosis is a rare condition that causes small patches of swollen tissue (called granulomas) to develop in the body[3]. Whilst any organ can be affected, lung involvement occurs in 90% of patients with sarcoidosis; this is also known as 'pulmonary sarcoidosis[4]. Other commonly affected areas include the skin, the eyes and lymph nodes. Symptoms include tender bumps on the skin, shortness of breath and a persistent dry cough[3].

The cause of sarcoidosis is unknown, although it is thought to be an autoimmune condition, caused by an inflammatory response to an environmental agent or infection[4]. The resulting inflammation causes granulomas to develop in the organs[3]. Sarcoidosis can affect people of any age, but it most commonly starts in people aged between 30 years and 40 years[3]. It is also more common in women[3].

The prognosis is generally good and although symptoms may come and go, in many people sarcoidosis will go away without treatment within a few years[3]. However, for some people the condition might slowly get worse over time, and might damage their organs[3], about 25% of people will develop residual fibrosis in the lungs or elsewhere. Treatment options are discussed under 'Current treatment options and relevant guidance' below.

Tumour necrosis factor (TNF) is a pro-inflammatory cytokine thought to accelerate the inflammatory process in sarcoidosis through its role in maintenance of granuloma formation. Thus, using agents that block the effect of TNF, such as infliximab, may be beneficial in treating sarcoidosis[5].

Incidence/prevalence

Around 1 in every 10,000 people in the UK have sarcoidosis[6]. Nine out of 10 people have sarcoidosis that affects their lungs (pulmonary sarcoidosis)[6]. Sarcoidosis may remit spontaneously or upon treatment but it has a chronic course in about 25% of patients[7].

Clinicians in Wales consulted by AWTTC estimated that 6 people in Wales would be likely to be eligible to start infliximab treatment for refractory pulmonary sarcoidosis each year.

Current treatment options and relevant guidance

There is currently no cure for sarcoidosis[6]. In most patients (around 60%), sarcoidosis will get better without treatment[6]. There are no guidelines for treatment. In Wales, refractory pulmonary sarcoidosis that has not responded to corticosteroids or other immunosuppressants is currently treated with add-on infliximab through application to the IPFR process.

The British Thoracic Society (BTS) Clinical Statement on pulmonary sarcoidosis acknowledges that the current evidence for treatment is weak[5]. It states that because of the need to minimise treatment-related morbidities in sarcoidosis, treatment should be started only of there is:

- potential danger of a fatal outcome or permanent disability; or
- unacceptable loss of quality of life[5].

The BTS Statement says although there is no good evidence for any medicine regimen in sarcoidosis, most patients who need treatment should start with corticosteroids (such as prednisolone)[5]. If corticosteroid treatment is not working then methotrexate (oral or subcutaneous) should be offered as the first choice of second-line medicine. Other second-line options include mycophenolate, leflunomide and azathioprine. Biological medicines are considered third-line therapeutic agents, to be started only after the failure of second-line treatment. Infliximab is the most common biological medicine used as third-line treatment of pulmonary sarcoidosis[5].

An international panel of 26 experts in the treatment of sarcoidosis agreed a consensus statement for a treatment algorithm in pulmonary sarcoidosis[8]. The recommendations were similar to the BTS guidance above.

Clinicians in Wales informed AWTTC that they follow the Royal Brompton & Harefield NHS Foundation Trust guidelines for the use of infliximab for the treatment of sarcoidosis in adults[2]. The guideline outlines the use of infliximab as a third-line treatment when corticosteroids and other immunosuppressants have failed. The dosing protocol to be used is 3 mg/kg at Weeks 0, 2, 6 and then every 8 weeks afterwards. If necessary the dose may be increased on consultant decision to 5 mg/kg if only a minimal improvement has been observed by the fourth dose[2]. Concomitant administration with an immunosuppressant is recommended, usually the immunosuppressant the patient was currently taking, to reduce the risk of them developing antibodies to infliximab, which are associated with an increased frequency of infusion reactions[2].

Outcome measures include an improvement in symptoms, improvement or stabilisation of pulmonary or cardiac function, quality of life and possible reduction in oral corticosteroid dose[2]. The patient's response to therapy is assessed after 6 months and if the patient has shown no improvement, infliximab will be discontinued[2].

Summary of evidence on clinical effectiveness

AWTTC conducted a literature search and identified one systematic review, two randomised controlled trials (RCTs) and 10 retrospective or observational studies. The review and studies are summarised below.

Systematic review

Adler et al. (2019) conducted a systematic review of the efficacy and safety of anti-tumour necrosis factor medicines in the treatment of sarcoidosis[9]. The review identified 5 RCTs, 6 RCT subset analyses, 3 non-randomised trials and 2 subset analyses, and 49 observational studies[9].

Two of the RCTs were studies of infliximab patients with pulmonary sarcoidosis (Baughman et al., 2006 and Rossman et al., 2006; discussed further below)[9]. One study showed that infliximab modestly improved vital capacity; the other study failed to show a similar result. The non-randomised studies in pulmonary sarcoidosis suggested that infliximab may improve pulmonary function[9].

In 13 non-randomised studies of infliximab (3 mg/kg to 5 mg/kg given every 4–8 weeks, apart from one study), pulmonary function tests showed improvements in 78.7% of patients (74 of 94 patients), pulmonary symptoms improved in 75.0% (24 of 32), and radiographic imaging improved in 52.2% (36 of 69)[9]. In an open-label study, percentage predicted forced vital capacity (FVC) increased by 6.6% ($p = 0.0007$) after 26 weeks of infliximab (5 mg/kg every 4 weeks) in 28 patients treated for pulmonary sarcoidosis as the main indication. Several studies demonstrated significant effects of infliximab on disease activity as measured by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) and levels of soluble interleukin-2 receptor[9].

Randomised controlled trials

Baughman et al. (2006) conducted a phase 2, multicentre, randomised, double-blind, placebo-controlled study in 138 patients from the USA and Europe with chronic pulmonary sarcoidosis[10]. Patients were randomised 1:1:1 to receive intravenous infusions of infliximab (3 mg/kg or 5 mg/kg) or placebo at Weeks 0, 2, 6, 12, 18, and 24, and were followed up to Week 52. Most patients in each treatment group received concomitant treatment with corticosteroids, some received an immunomodulator only and some received both[10].

The primary endpoint was change from baseline in the percentage of predicted forced vital capacity (FVC) at Week 24[10]. The main secondary endpoints included the Saint George's Respiratory Questionnaire (SGRQ) total score, 6-min walk distance (6-MWD) test, and Borg's CR10 dyspnoea score (before 6-MWD test)[10].

Patients who received infliximab had a least squares mean increase of 2.5% from baseline to Week 24 in the percentage of predicted FVC, compared with no change in patients who received placebo ($p = 0.038$)[10]. The authors concluded that the clinical importance of the 2.5% improvement was unclear, particularly because no treatment benefit was demonstrated for the other major secondary endpoints. Results of post-hoc analyses suggested that patients who had more severe disease tended to benefit more from infliximab treatment[10].

Treatment benefit was not demonstrated in the secondary endpoints of SGRQ, 6-MWD, or Borg's CR10 dyspnoea score in the overall study population[10]. The SGRQ total score improved in all groups at Weeks 24 and 52, with no significant differences between the groups[10].

Rossman et al. (2006) conducted a double-blind, randomised, placebo-controlled phase II study to assess the efficacy of infliximab in treating active pulmonary sarcoidosis[11]. Inclusion criteria included patients with previous or current treatment with corticosteroids who needed another treatment added based on either suboptimal response or intolerance of corticosteroids. In the study's first phase, patients were stratified according to corticosteroid use and randomised in a 2:1 ratio to receive infliximab 5 mg/kg ($n = 13$) or placebo ($n = 6$) at Weeks 0 and 2. The major endpoint was at Week 6. The second phase consisted of 2 open-label infusions for all patients at Weeks 6 and 14, and a 24-week follow-up period. The study aimed to include 42 patients, but due to lack of enrolment only 19 patients were treated and only 16 completed the study[11].

Most patients in both treatment groups (69% and 67%) were taking corticosteroids at baseline; the infliximab group was taking a higher dose for a longer time than the placebo group (23.8 mg and 850 days versus 8 mg and 335 days)[11]. At Week 6 the mean relative change in vital capacity compared to baseline was 15.22 (± 9.91%) for patients who received infliximab and 8.39 (± 3.33%) for patients who received placebo; however, the difference was not statistically significant ($p=0.65$). Patients in both groups appeared to have improved function between Weeks 6 and 14, when both groups received open-label infliximab, followed by stable function when infliximab was stopped. Two patients receiving infliximab showed a 15% improvement in predicted vital capacity; no patients in the placebo group had the same improvement by Week 6. Changes in vital capacity in patients who received infliximab in phase I and II of the study showed a significant improvement compared with baseline ($p<0.02$)[11].

There were no differences in quality of life, measured by the SF-36 questionnaire, between patients in the infliximab group and those in the placebo group at baseline; SF-36 scores were similar at Week 6[11].

An overview of 10 observational studies can be found in Appendix 1.

Safety

In the RCT conducted by Baughman et al. the proportions of patients who had adverse events were similar across the treatment groups. The most common adverse events reported were respiratory system disorders, mostly upper respiratory tract infection, coughing, dyspnoea and bronchitis[10]. The proportions of patients who discontinued treatment due to an adverse event were low: 2 of 44 patients in the placebo group and 5 of 91 patients in the combined infliximab groups. Up to Week 24, serious adverse events had occurred in 5 of 44 patients in the placebo group and in 10 of 91 patients in the infliximab group. The pattern was similar up to Week 52. The incidence of infusion reactions (2.3%) was the same in the placebo group as in the combined infliximab groups[10].

Safety data from the Rossman et al. RCT were similar. The study showed no difference in the percentage of adverse events between the two treatment groups (92% for infliximab and 100% for placebo)[11]. More serious adverse events occurred in the infliximab group (31% versus 17%). Serious adverse events were reported in one patient in the placebo group and in four patients in the infliximab group (one patient had decreased white blood cell count and elevated creatinine phosphokinase; one had pneumonia; one had visual defect; and one patient developed cellulitis, acute renal failure, pulmonary embolus and died)[11].

The Summary of Product Characteristics (SmPC) for infliximab (Remicade®) lists contraindications; these include: tuberculosis, sepsis, abscesses, other severe opportunistic infections, and patients with moderate or severe heart failure (NYHA class III/IV)[1]. Infliximab should be used with caution in patients who have mild heart failure (NYHA class I/II) and closely monitored; infliximab must be discontinued if any new or worsening symptoms of heart failure develop[1].

The SmPC warns about acute infusion-related reaction, including anaphylactic shock and delayed hypersensitivity reactions[1]. Infliximab increases susceptibility to serious infections, such as tuberculosis, bacterial infections (including sepsis and pneumonia), also fungal, viral and other infections. When being treated with infliximab patients must be monitored closely for infections (including tuberculosis) before, during and after treatment (for at least 6 months). If a serious infection or sepsis develops infliximab treatment should be stopped. Caution is needed when considering infliximab for patients with chronic or recurrent infections, including concomitant immunosuppressive therapy, and the infection risk when treating older people with infliximab[1].

The SmPC lists very common adverse reactions (occurring in ≥ 1 in 10 people) as: viral infection (such as influenza, herpesvirus infection), headache, upper respiratory tract infection, sinusitis, abdominal pain, nausea, infusion-related reaction and pain[1].

Discussion

The evidence in this report for the use of infliximab in refractory pulmonary sarcoidosis comes from two phase II RCTs of infliximab (one of which closed early due to lack of enrolment), one systematic review and a series of observational studies.

As previously stated, clinicians in Wales informed AWTTC that they follow the Royal Brompton guideline for dosing. The patient's response to therapy would be assessed after 6 months and if no improvement shown then infliximab would be discontinued[2].

All patients in the study by Baughman et al. (2006) were taking stable background corticosteroid and/or immunosuppressant therapy, and did not need to have active or refractory sarcoidosis to enrol in the study[10]. In the Rossman et al. study, patients needed to be on stable corticosteroids for two weeks and the trial was underpowered to detect a treatment difference due to poor uptake[11]. These factors may account in part for the low response across the two trials. The authors of the systematic review argue that the use of percentage predicted FVC as a primary endpoint is restrictive in the face of the complexity of pulmonary sarcoidosis and may have limited the trials' ability to demonstrate efficacy[9].

The uncontrolled observational studies were conducted in patients with refractory sarcoidosis, and most had small sample sizes. Most studies showed improvements in FVC or VC and other lung function outcomes that were greater than those seen in Baughman et al. study. Patients with more severe and active disease tended to demonstrate greater response to infliximab.

A NICE evidence summary (published in 2016) stated then that immunosuppressants have a limited role in pulmonary sarcoidosis because there were not enough high-quality studies to confirm how well they worked and they have significant adverse effects[4]. The minimally clinically important changes for sarcoidosis are unclear, although in people with severe and active refractory disease, even stabilisation of lung function may be preferable to further deterioration[4]. An NHS England Clinical Commissioning Policy published in 2018 for infliximab to treat progressive pulmonary sarcoidosis in adults did not recommend it to be routinely commissioned, based on the available evidence at that time[12]. The systematic review and four of the observational studies identified during the literature search have been published since 2018. The 2019 systematic review concluded that there was limited evidence of efficacy of infliximab in (pulmonary) sarcoidosis[9]. Alternative biologics were not recommended based on available data. Larger prospective studies are needed.

Cost-effectiveness evidence

Background

AWTTC conducted a literature search but no cost-effectiveness studies of infliximab in the treatment of sarcoidosis were identified.

Budget impact

Clinicians in Wales estimated that 6 patients each year with refractory pulmonary sarcoidosis may be eligible for treatment with infliximab. Most of them would continue treatment if the therapy is available. They confirmed that the dosing protocol they

would use is 3 mg/kg at Weeks 0, 2, 6 and then every 8 weeks afterwards[2]. If necessary the dose may be increased on consultant decision to 5 mg/kg if only a minimal improvement has been observed by the fourth dose. Patients would be reviewed after 6 months (5 doses) and treatment discontinued if there had been no response, otherwise continued for a further 18 months (14 doses in total).

Table 1. Estimated costs for treatment with infliximab per patient in Wales

	Medicine cost for one treatment	Cost of administering one treatment†	Total treatment cost per patient		
			6 months	12 months	24 months
Infliximab* (3 mg/kg)	¶¶	£527	¶¶	¶¶	¶¶
Infliximab* (3 mg/kg then 5 mg/kg)	3 mg/kg: as above; 5 mg/kg: ¶¶	£527	¶¶	¶¶	¶¶

*Confidential NHS Wales contract price plus VAT, using lowest and mid-range price and the average weight for a British adult (77.25 kg)[13,14]. Assumes vial wastage.
† 2020-2021 National Schedule of Reference Costs: assumes 'Deliver Simple Parenteral Chemotherapy at first attendance' (HRG code SB12Z) for the first dose, followed by 'Deliver Subsequent Elements of a Chemotherapy Cycle' for the other two doses (HRG code SB15Z)[15]. £527 for initial administration and £471 for subsequent treatments.

Table 2. Estimated costs for infliximab* treatment for patients in Wales

	Year 1†	Year 2†	Year 3†
Number of patients	6	11	11
Overall net cost	¶¶	¶¶	¶¶

* Assuming all patients taking 3 mg/kg dose, and 6 new patients starting treatment each year and 1 patient discontinuing treatment (after 6 months) each year.
† Confidential NHS Wales contract price plus VAT, using lowest and mid-range price and the average weight for a British adult (77.25 kg)[13,14]. Assumes vial wastage.

Budget impact issues
Infliximab biosimilar NHS Wales contract costs have been used in the calculations, costs may be higher for other products.

Table 2 includes costs based on the lower dose range, costs will be slightly higher for those patients escalating to the 5 mg/kg dose.

The budget impact has not considered mortality rates. Costs of additional screening and monitoring for bacterial, viral and fungal infections and adverse event costs are also excluded from the budget impact. The budget impact therefore may be higher than predicted.

Clinical experts have said that patients may remain on treatment for 2 years after which time patients would be taken off treatment, or may discontinue treatment after 6 months if the disease does not respond. One patient is expected to stop treatment after 6 months per year. It is assumed that 6 new patients will commence on treatment each year. As this number is not anticipated to grow over the next few years, from Year 2 onwards there are anticipated to be 11 patients receiving treatment each year.

The budget impact is likely to be lower for Year 1 than estimated given that the majority of patients are already receiving treatment through IPFR.

Additional factors

Prescribing unlicensed medicines

Infliximab is not licensed to treat this indication and is therefore prescribed ‘off label’. Providers should consult relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

References

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Appendix 1

Table 4. Summary of observational studies

Reference	Study details	Main results
Sakkat et al. (2022)[16]	A retrospective cohort study at 3 sites (2 in the UK). **Population** 33 patients with refractory sarcoidosis. All patients had been treated with corticosteroids and at least one other immunomodulator. Of 30 patients with lung involvement, **14 patients** were treated with infliximab for pulmonary symptoms. **Dosage** Patients received infliximab 3 mg/kg to 5 mg/kg at Weeks 0, 2, and 6. After this, infliximab was given every 4–8 weeks.	Treatment success was defined as increase in absolute FVC or forced expiratory volume in 1 second (FEV1) by > 10% or no change in FVC or FEV1 (±10% from baseline). In the 14 patients with pulmonary symptoms treatment success was 78.6% (95% CI: 49.2–95.3). In the whole study group of 33 patients, adverse events were reported in 25 patients; 7 patients discontinued treatment due to an adverse event. The most common adverse events were pneumonia (6 patients), leukopenia (5 patients), infusion reaction (4 patients), minor infection (3 patients), paraesthesia (2 patients) and anaphylaxis (4 patients).
Peters et al. (2021)[17]	A single centre retrospective cohort study in the Netherlands, of the effect of switching to Flixabi® (a biosimilar of infliximab). **Population** 79 patients with severe refractory sarcoidosis who were receiving Remicade® or Inflectra® maintenance treatment. Patients had been receiving infliximab for mean of 4.4 years; **41 patients** had pulmonary sarcoidosis as the main indication.	No patients discontinued infliximab in the first six months after switching (the study's primary endpoint). Out of the whole study group of 79 patients, 3 reported an adverse event related to Flixabi®. No major adverse events were reported and no patients had infusion reactions. For the 41 patients with pulmonary sarcoidosis, there were no differences between baseline pulmonary function before and after the switch to Flixabi® . After switching an improvement of 7 ± 13 points was found for physical functioning as measured using the RAND/SF36 (p = 0.002).

Reference	Study details	Main results
	Dosage Patients received infliximab every 4 weeks (n =55), 5 weeks (4), 6 weeks (12), 7 weeks (2) and 8 weeks (6).	
Kullberg et al. (2020)[18]	A study of changes in lung cells during infliximab treatment. **Population** 13 patients in Sweden with refractory sarcoidosis. Patients had received previous treatment with corticosteroids and/or methotrexate. In **11 patients** infliximab treatment was indicated for pulmonary sarcoidosis. **Dosage** Patients were given 3 mg/kg to 5 mg/kg infliximab every 4–8 weeks after initial induction; the dose was later changed to 5 mg/kg for all patients.	Ten patients were classed as responders to treatment and 2 patients who had deteriorating disease were classed as non-responders. Responders showed an increase in mean percentage of predicted FVC from 70 to 80%, and mean percentage of predicted FEV1 from 59 to 67% at follow-up ($p < 0.05$ for both). The mean percentage of DLCO increased from 69 to 74% in responders, but this did not reach significance. Infliximab treatment was well tolerated with no adverse events, except for one patient who developed a probable adverse event with liver toxicity.
Schimmelpennink et al. (2019)[19]	A retrospective cohort study in the Netherlands to investigate the use of 18F-FDG PET/CT to measure lung disease activity. **Population** **27 patients** who were started on infliximab for refractory pulmonary sarcoidosis. **Dosage** Patients received infliximab monthly (every 4 weeks) at dose of 5 mg/kg, starting at Week 0, 2 and then every 4 weeks.	Lung function was assessed before and after 6 months of infliximab treatment. After 6 months of infliximab, FVC and FEV1 significantly increased: +4.6% and +5.1% predicted, respectively ($p = 0.009$ and $p = 0.001$). The carbon monoxide diffusing capacity (DLCOc) increased by 2.4%; however, this did not reach statistical significance.

Reference	Study details	Main results
Jamilloux et al. (2017)[7]	A retrospective multicentre study. **Population** 132 patients with refractory sarcoidosis – defined as failing at least 1 immunosuppressant. **14 patients** had pulmonary sarcoidosis as main treatment indication. **Dosage** 120 patients (91%) were treated with infliximab: 3–5 mg/kg infusions given at weeks 0, 2 and 6, then every 4–8 weeks. 8 patients received adalimumab, 3 patients received etanercept and 1 patient received certolizumab pegol. Median follow-up was 20.5 months.	Clinical improvements were seen in 64% of all patients treated with anti-TNF medicines. 24 (18%) had a complete response and 61 (46%) had a partial response. No significant difference was seen between anti-TNF medicine given alone or given with an immunosuppressant. Similar results were seen in subgroup analyses of patients with refractory sarcoidosis (n = 125) and severe sarcoidosis (n = 122), except for 'upper respiratory tract involvement' (p = 0.058). Pulmonary involvement was associated with a lower clinical response to an anti-TNF medicine; ePOST improvement was not statistically significant (p = 0.46). No pulmonary function tests were performed. In a multivariate analysis, comparing responders (complete or partial response) with non-responders (stable or progressing disease), only pulmonary involvement was associated with a lower clinical response to anti-TNF (OR = 0.38; 95% CI: [0.14–0.92]; p = 0.03). Of all patients treated with an anti-TNF, 69 patients (52%) experienced 130 adverse events to an anti-TNF that required discontinuation of treatment in 31 patients. The most frequent adverse events were infections (90 cases in 47 patients, of which 25 needed hospitalisation or treatment interruption). 9 patients had severe allergic reactions; eight of them with infliximab. At the end of follow-up 75 patients were still receiving an anti-TNF medicine; 57 patients had stopped treatment

Reference	Study details	Main results
		because of adverse events, lack of efficacy, favourable outcome or personal reasons.
Vorselaars et al. (2015)[20]	A prospective, open-label cohort study conducted in the Netherlands. **Population** 56 active refractory sarcoidosis patients with severe sarcoidosis, unresponsive to first- and second-line treatment, or who have experienced severe side effects from these medicines. **34 patients** had pulmonary sarcoidosis as their main symptom. **Dosage** Infliximab given at dose of 5 mg/kg at Weeks 0 and 2 and then every 4 weeks over a period of 6 months.	In patients with a pulmonary treatment indication, FVC increased by 6.64% ($p = 0.0007$), FEV1 increased by 5.80% ($p < 0.0001$) and DLCOc increased by 4.12% ($p = 0.001$) after 6 months of infliximab treatment. An improvement of $\geqslant$ 5% FVC and FEV1 was seen in 71% and 64% of patients, respectively. In 46% of patients this increase exceeded 10%. Severe side effects leading to discontinuation of treatment were reported in 6 patients (3 pneumonia; 1 severe progressive disease; 1 peritonitis; 1 severe gastrointestinal complaint); 2 later died. Two patients formed antibodies against infliximab and were switched to adalimumab. One patient discontinued treatment for an undisclosed reason. 13 patients had mild adverse effects.
Wijnen et al. (2014)[21]	A study of gene variant and response to anti-TNF medicines, conducted in the Netherlands. **Population** 118 patients with refractory sarcoidosis who had failed corticosteroids and methotrexate. **69 patients** had pulmonary sarcoidosis as their main symptom. **Dosage** 76 patients were treated with infliximab, including 46 patients with lung involvement. Mean infliximab dose	Data available for 111 patients (7 patients discontinued treatment within 1 year). In 39 (56.5%) out of the 69 patients with RFI at least one lung function test parameter improved by >10%. Overall, 83 (74.8%) of the 111 included patients with refractory sarcoidosis had a positive response. The use of infliximab or adalimumab had no influence on outcome, both medicines resulted in 25% non-responders. Nine (8.1%) patients formed antibodies against infliximab and were switched to adalimumab (n = 4) or had to

Reference	Study details	Main results
	was 404.1 ± 25.5 mg; mean dose interval 4.5 ± 0.6 weeks.	discontinue TNF-inhibitor treatment (n = 5). None of the patients developed antibodies against adalimumab. Adverse events were seen in 14 (12.6%) out of 111 patients treated with TNF inhibitors. Documented adverse events were minor infections (n = 11), sepsis (n = 1) and herpes zoster infection (n = 5). Two patients had infusion reactions. **Quality of life** Fatigue, measured by the fatigue assessment scale, improved in 60 out of 100 patients assessed.
Van Rijswijk et al. (2013)[22]	A retrospective cohort study conducted in the Netherlands. **Population** 45 evaluable patients refractory to regular medication (corticosteroids and/or methotrexate) or who had severe side effects to them. **23 patients** had pulmonary sarcoidosis as main indication. **Dosage** Infliximab given at a dose of 5 mg/kg at weeks 0, 2, 6, 10, 14 and 18.	Results reported for pulmonary subgroup (n=23); these patients had significantly worse pulmonary function and higher Scadding stages* than patients with an extrapulmonary treatment indication. The subgroup analysis showed a larger increase in pulmonary function tests in the 23 patients who had a pulmonary main indication for initiating treatment. The changes in percentage of predicted VC, percentage of predicted FEV1 and percentage of predicted DLCOc were respectively 7.6% ($p < 0.0001$), 7.9% ($p < 0.0001$) and 3.5% of predicted ($p = 0.011$). In this pulmonary subgroup, 52% of patients had a relative improvement in VC of 10% or more. Adverse events reported for whole group, showed that infliximab was generally well tolerated. Only a few adverse events were documented and most were mild. One patient was hospitalised because of pneumonia. There was one case of a severe infusion reaction during cycle 1–6 which forced discontinuation of treatment.

Reference	Study details	Main results
		Quality of life Fatigue and physical functioning scores were available in 27 patients (60%). Analysis showed a statistically significant change in fatigue severity scores (–5.3; p = 0.003) as well as in the physical functioning scores (+ 12.6; p = 0.011).
Russell et al. (2013)[23]	A retrospective study conducted in the USA. **Population** 26 patients with refractory sarcoidosis who were started on infliximab because of failure or intolerance of treatment with corticosteroids or other immunosuppressant. Of these, **15 patients** had pulmonary symptoms as main indication. **Dosage** An escalation in infliximab dosing was required for the majority of patients, with an average maximum infliximab dose of 511 mg (range 300–1000 mg) and an average dosing frequency of every 5.5 weeks (range every 4–6 weeks).	There was a small average improvement in the FEV1, FVC and TLC in patients with pulmonary sarcoidosis (2%, 4%, and 11% improvement, respectively). These results did not reach statistical significance. There was no appreciable difference in DLCO either before or after initiation of infliximab in this group. In a subgroup analysis of the pulmonary sarcoid patients with abnormal pulmonary function tests before starting infliximab therapy, there was a mild improvement in the average FEV1 (3% increase), FVC (5% increase) and DLCO (5% increase). There was a statistically significant improvement in the TLC of 17% after starting infliximab in this subgroup analysis. Adverse events were seen in 57.7% of all patients treated with infliximab over a combined duration of therapy of 46.2 months. Three patients had adverse events that needed permanent discontinuation of infliximab; these were severe pneumonia, a positive tuberculosis skin test and recurrent sinusitis attributed to infliximab use. The most commonly reported adverse events were minor infection, rash and pneumonia (19.1%, 19.1% and 14.3%, respectively).

Reference	Study details	Main results
Hostettler et al. (2012)[24]	A retrospective chart review of long-term treatment with infliximab in Switzerland. **Population** 28 patients with chronic steroid-resistant (or refractory to steroid-sparing medicines or who had severe side effects on these) sarcoidosis who were treated with infliximab. 16 patients were treated for >12 months (long-term); of these, **5 patients** had pulmonary sarcoidosis as main indication. **Dosage** All patients received intravenous infusions of infliximab, typically 3 mg/kg, in 4-weekly, 6-weekly or 8-weekly intervals. During infliximab treatment, patients remained on their concomitant medication with oral corticosteroids and/or other immunomodulatory drugs, at a minimum dose of typically 5 mg prednisone and 50 mg of azathioprine per day.	One out of 5 patients with predominantly pulmonary sarcoidosis showed a >10% improvement in percentage predicted FVC; 3 of 5 showed a 0–10% improvement; and in 1 of 5 patients, percentage predicted FVC% declined. during infliximab treatment. Mean improvement in percentage predicted FVC was 6% (range –6 to 23). At baseline, absolute FVC values ranged from 0.94 to 3.63 litres (mean 2.26 ± 1.25). After infliximab treatment, absolute FVC values ranged from 0.77 to 4.28 litres, with the mean FVC slightly increasing to 2.57 ± 1.58 litres. 15 of 16 patients tolerated long-term infliximab treatment without any clinically relevant side effects. One patient had a possible adverse event after 4 years of treatment, when they developed a symptomatic bradyarrhythmia 6 h after infliximab infusion. None of the 16 patients developed severe infections of malignancies during infliximab treatment.
Orum et al. (2012)[25]	A retrospective study conducted in Denmark. **Population** 12 patients with refractory sarcoidosis receiving infliximab as a 3rd-line treatment; **9 patients** had pulmonary sarcoidosis as main indication.	All 9 patients with pulmonary symptoms obtained an average increase in FEV1 (5.12%), FVC (3.20%) and TLC (0.9%) after 7 treatments with infliximab. Diffusion capacity for carbon monoxide (TLCO) unexpectedly decreased compared with baseline value (−1.63%). After the last treatment, there was a mean increase in all pulmonary parameters in all patients compared with baseline

Reference	Study details	Main results
	Dosage Initial dose was 3 mg/kg in 11 patients and 5 mg/kg in 1 patient. During treatment 2 patients had dose increased to 5 mg/kg. Treatment was given at weeks 0, 2 and 6, and then at 8-week intervals. Mean duration was 25 months (3–56).	values (4.38%, 7.12%, 5.68%, 7.10%), although this increase was too low to be of any certain clinical significance. No side effects were reported.

CI: confidence interval; DLCOc/DLCO: carbon monoxide diffusing capacity; ePOST: extrapulmonary physician organ severity tool; 18F-FDG PET/CT: fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography; FEV: forced expiratory volume; FEV1: FEV in 1 second; FVC: forced vital capacity; RAND/SF36: RAND short form survey– 36 item; RFI: respiratory functional impairment; TLC: total lung capacity; TLCO: transfer factor for carbon monoxide; TNF: tumour necrosis factor; VC: vital capacity

*Scadding stages: 0: normal; I: enlarged nodes only; II: enlarged nodes and parenchymal changes; III: parenchymal changes without enlarged nodes or fibrosis; IV: fibrosis[5]