

NHS England

**Evidence review: Infliximab for refractory
neurosarcoidosis**



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The content of this evidence review was up-to-date in August 2018. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Key points

Regulatory status: Infliximab is licensed for treating rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis. Use of infliximab for any manifestation of sarcoidosis is off-label. Infliximab is administered as an intravenous infusion.

Overview

This evidence summary considers the best available evidence for infliximab (alone or in combination with other medicines) for treating neurosarcoidosis that is refractory to standard treatments (for example, corticosteroids and immunosuppressants) or is progressive despite current treatments. Sarcoidosis is characterised by the presence of non-caseating granulomas (lumps caused by clusters of inflammatory cells) in the organs. Neurosarcoidosis is a rare type of sarcoidosis that affects the central nervous system (CNS, brain and spinal cord). Symptoms of neurosarcoidosis include meningitis and vasculitis.

The evidence review focusses on 2 multicentre retrospective case reviews undertaken in the USA (Gelfand et al. 2017, n=66) and France (Jamilloux et al. 2017, n=132, 63 with neurosarcoidosis). In summary, the results of the studies suggest that infliximab can improve outcomes for some people with refractory or progressive neurosarcoidosis, with many people reported as experiencing a complete or partial response. However, some people had residual symptoms and functional impairment after treatment, or experienced no response to treatment. Also, adverse effects of infliximab were sometimes serious and led to hospitalisation or discontinuation of treatment. Relapse of neurosarcoidosis appears to be common on stopping infliximab. See below for more details.

When assessing images obtained using magnetic resonance imaging (MRI), Gelfand et al. found that, in people using infliximab for 1.5 years on average, neurosarcoidosis resolved completely in 52% (29/56), partially improved in 30% (17/56), stayed the same in 14% (8/56) and got worse in 4% (2/56). When people were assessed by their specialist after using infliximab, Gelfand et al. found that clinical signs and symptoms of neurosarcoidosis resolved completely in 29% (19/66), partially improved in 48% (32/66), stayed the same in 18% (12/66) and got worse in 3% (2/66). A favourable response with complete or partial recovery was seen in 80% of people (45/56) who had evaluations for both clinical response and MRI findings. This suggests that 8 out of 10 people experienced some improvement in both findings on MRI and clinical signs and symptoms.

In the study by Gelfand et al., neurosarcoidosis recurred in 56% of people (9/16) who had experienced remission after using infliximab for, on average, 1.5 years. Relapse occurred, on average, about 6 months after treatment was stopped. These results suggest that around half of people with neurosarcoidosis experience relapse when they have been treated with infliximab for about 1.5 years.

In the study by Jamilloux et al., a tool was used to assess the severity of sarcoidosis in various organs in the body. The average severity score for the CNS changed from 3.78 to 2.62 after treatment with an anti-TNF (usually infliximab) in 63 people with neurosarcoidosis (p=0.001). This shows that people's score improved by 1.16 on a 6-point scale, which

suggests that, on average, their neurosarcoidosis improved. However, although individual people may feel quite a large benefit, others may experience no benefit, and it is unclear if a 1 point improvement is large enough to be important to the overall population with neurosarcoidosis.

Overall, the studies suggest that, when infliximab is used for neurosarcoidosis, its adverse effects are similar to those that are seen when it is used for the licensed indications, as listed in the summary of product characteristics; for example, infections are common and may lead to hospitalisation or discontinuation of treatment.

The results of the studies should be interpreted with caution because the studies are small, uncontrolled, and did not use standardised treatment and monitoring protocols. Weaknesses in the studies' design and conduct mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions.

The optimal treatment regimen for infliximab for treating neurosarcoidosis is unclear because treatment regimens varied within and between the studies. The dosage of infliximab typically used was 3 to 7 mg/kg at weeks 0, 2, and 6, then every 6 to 8 weeks. The median duration of treatment in the key studies was between about 1.5 years and 1.7 years. Most people in the studies took corticosteroids and/or immunosuppressants in combination with infliximab, and it is unclear how this affects outcomes. It is also unclear what potential factors predict a good response to infliximab treatment.

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1. Introduction

Background and current guidance

Sarcoidosis can present in a wide variety of ways, ranging from mild, acute self-limiting disease to chronic disease involving several organs and causing severe symptoms and functional impairment. It is characterised by the presence of non-caseating granulomas (lumps caused by clusters of inflammatory cells) in the organs. The lungs are affected in more than 90% of people with sarcoidosis. The skin, eyes, nervous system, liver and heart can also be affected (Sarcoidosis, [Oxford Textbook of Medicine](#)).

The cause of sarcoidosis is unknown, although it may be due to an inflammatory response to an environmental agent or infection. In the UK, the incidence of the condition is estimated to be about 3/100,000 person-years, based on general practice data ([British Thoracic Society \(BTS\) Interstitial lung disease guideline 2008](#)). According to [Sarcoidosis UK](#), most specialists agree that around 1 in every 10,000 people have sarcoidosis in the UK. Every year in the UK about 3,000 to 4,000 people are diagnosed with sarcoidosis. Sarcoidosis can occur at any age, but commonly affects adults in their 30s or 40s.

Neurological sarcoidosis occurs in about 5% of people with sarcoidosis and is, therefore, uncommon (about 20 cases per million people). It can affect the central nervous system (CNS, brain and spinal cord) and peripheral nervous system (including the 12 cranial nerves in the head and neck). For the purpose of this evidence summary, neurosarcoidosis refers to sarcoidosis affecting the CNS. About half of people with neurosarcoidosis have a cranial neuropathy causing symptoms such as weakness or numbness of the face, problems with hearing, weakness of the tongue, difficulty swallowing or double vision. The rest have more serious disease affecting the CNS, such as meningitis (inflammation of the lining of the brain and spinal cord) or vasculitis (inflammation of the blood vessels in the brain) ([Sarcoidosis and the nervous system, Sarcoidosis UK](#)).

The natural course of sarcoidosis is difficult to predict and there are significant differences in the severity of disease and the organs involved. The prognosis is generally good and sarcoidosis resolves in most people within 2 to 5 years. However, about 25% of people will develop residual fibrosis (thickening and scarring) and, in some cases, the disease will become chronic and persist for more than 5 years. Disease-related mortality is reported to be about 5%, with the most common causes of death being from lung, cardiac and neurological disease that is refractory to therapy (Sarcoidosis, [Oxford Textbook of Medicine](#)).

There is no national guidance on managing sarcoidosis. Treatment is not recommended for everyone because of the high rate of spontaneous remission and the risk of adverse effects. The treatment decision is usually based on symptoms, the extent of symptomatic disease, whether the sarcoidosis is acute or chronic, and the risk of life-threatening complications. First-line treatment is usually with corticosteroids such as prednisolone. Other treatments that may be added if the disease does not respond include methotrexate, chloroquine, hydroxychloroquine, leflunomide and infliximab (Sarcoidosis, [Oxford Textbook of Medicine](#)).

Unpublished data suggests about 100 people are diagnosed with neurosarcoidosis affecting the brain and spinal cord in the UK each year. Of these, around 80% respond to

conventional oral treatment but around 20% (20 people) need further treatment, such as infliximab.

This evidence summary considers the best available evidence for infliximab (alone or in combination with other medicines) for treating neurosarcoidosis that is refractory to standard treatments (for example, corticosteroids and immunosuppressants) or progressive despite current treatments.

Product overview

Mode of action

Infliximab is a biological human monoclonal antibody, which inhibits tumour necrosis factor (TNF) alpha (a cell signalling protein or cytokine which is involved in systemic inflammation), thereby reducing disease activity ([infliximab summaries of product characteristics](#)).

Regulatory status

Infliximab is licensed for treating rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis (infliximab summaries of product characteristics). Use of infliximab for treating any manifestation of sarcoidosis is off-label.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using infliximab outside its authorised indications. [Supporting information and advice](#) is also available from the GMC.

At the time of publication, 4 infliximab products are available, the original brand [Remicade](#) and 3 biosimilar medicines, [Flixabi](#), [Inflectra](#) and [Remsima](#).

Dosing information

Dosing information varies for the licensed indications of infliximab and can be found in the summaries of product characteristics. Typically, across the licensed indications, the dose is 3 mg/kg or 5 mg/kg given as an intravenous infusion followed by additional infusions 2 and 6 weeks after the first infusion, then every 8 weeks as required, according to clinical response.

Dosing information for infliximab for neurosarcoidosis is discussed in the evidence review within this evidence summary.

2. Methodology

A description of the relevant Population, Intervention, Comparison and Outcomes ([PICO](#)) for this review was provided by NHS England's Policy Working Group for the topic (see the [literature search terms](#) section for more information). The research questions for this evidence review are:

1. Is infliximab clinically effective in the treatment of neurosarcoidosis, particularly disease that is refractory or progressive?

2. Is infliximab safe to use in the treatment of patients with neurosarcoidosis, particularly disease that is refractory or progressive?
3. Is infliximab a cost-effective treatment option for use in patients with neurosarcoidosis, particularly disease that is refractory or progressive?

The searches for evidence to support the use of infliximab for neurosarcoidosis were undertaken by the NICE Guidance Information Services' team. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on [search strategy](#) and [evidence selection](#).

The NICE [evidence summary: process guide](#) (2017) sets out the how the summaries are developed and approved for publication. The included studies are quality assessed using the National Service Framework for Long term Conditions (NSF -LTC) evidence assessment framework as set out in NHS England's Guidance on conducting evidence reviews for Specialised Services Commissioning Products (2016) (see the [grade of evidence](#) section for more information).

3. Summary of included studies

The evidence review primarily focusses on 2 multicentre retrospective case reviews undertaken in the USA (n=66) and France (n=132, 63 with neurosarcoidosis) and these studies are included in the [evidence summary tables](#).

The evidence review also gives a brief overview of 7 case series with outcomes for 5 to 9 people using infliximab for neurosarcoidosis. These are included to give an indication of the volume and quality of the evidence available; however, they have not been included in the main evidence tables because of their poor quality and high risk of bias.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Key evidence from larger prospective and retrospective studies including people with neurosarcoidosis treated with infliximab			

<p>Gelfand et al. 2017 Retrospective case review in 6 centres in the USA</p>	<p>66 people (mean age 47 years, 62% white) with probable (n=39, 59%) or confirmed (n=27, 41%) neurosarcoidosis on biopsy who had been treated with infliximab.</p> <p>65 people (98%) had previously been treated with glucocorticoids. When infliximab was started, 52 people (79%) were taking glucocorticoids</p> <p>52 people (79%) previously took at least 1 immunosuppressant. When infliximab was started, 52 people (79%) were taking an immunosuppressant, usually methotrexate (n=22, 33%), mycophenolate mofetil (n=18, 27%) or azathioprine (n=10, 15%)</p>	<p>Infliximab loading doses were typically given at weeks 0, 2 and 6</p> <p>Maintenance dosages were 3–7 mg/kg (most commonly 5 mg/kg) 4–8 weekly</p> <p>Median length of treatment 1.5 years</p> <p>No comparator</p>	<p>Clinical response: stability, improvement, or worsening of neurologic symptoms and signs at last follow-up</p> <p>A favourable response was defined as partial or complete improvement on MRI together with clinical stability, partial clinical improvement or complete clinical recovery</p>
<p>Jamilloux et al. 2017 Retrospective case review in 25 centres in France</p>	<p>132 people (median age 45 years, 45% white) with refractory sarcoidosis who had used an anti-TNF medicine. Infliximab was the first-line anti-TNF in 120 people (91%)</p> <p>Before anti-TNF initiation, 128 people (97%) had received corticosteroids and 125 people (95%) had received at least 1 immunosuppressant over a median duration of 16 months</p> <p>During anti-TNF treatment, 113 people (86%) received corticosteroids and 97 people (73%) received an immunosuppressant (usually methotrexate, n=81, 61%)</p> <p>63 people had neurosarcoidosis. It is unclear how many people with neurosarcoidosis were using infliximab</p>	<p>When infliximab was used, it was given at a dosage of 3–5 mg/kg at weeks 0, 2, and 6, then every 4–8 weeks</p> <p>Median follow-up 20.5 months</p> <p>No comparator</p>	<p>Change in ePOST scores</p>

Supplementary evidence from retrospective case reviews of 5 to 9 people with neurosarcoidosis treated with infliximab			
Hostettler et al. 2011 Retrospective case review in Switzerland	16 people (mean age 51 years, 100% white) with histologically confirmed chronic progressive sarcoidosis (mean duration 12 years) who either had steroid-resistant disease, were refractory to steroid-sparing treatment, or developed severe adverse effects with treatments, and who had been treated with infliximab for at least 12 months 13 people remained on concomitant medication with oral corticosteroids alone (n=6, 37%) or in combination with an immunosuppressant such as azathioprine (n=7, 44%) Neurosarcoidosis was the main treatment indication in 6 people	The dosage of infliximab was typically 3 mg/kg at 4, 6 or 8-weekly intervals Mean duration 29 months in all cases (36 months in people with neurosarcoidosis) No comparator	Treatment response (complete remission, partial remission or no response [not defined]) assessed by specialist clinicians
Leonhard et al. 2016 Retrospective case review in the Netherlands	52 people (median age 52 years, 54% white) with possible (n=14, 27%), probable (n=37, 71%) or definite (n=1, 2%) neurosarcoidosis, (categorised according to Zajicek's classification system, modified by Marangoni et al.) 7 people used infliximab, 1 person used infliximab and adalimumab and 1 person used infliximab and mycophenolate mofetil. All were taking corticosteroids	The dosage of infliximab was not reported Mean follow-up was 42 months No comparator	Response to treatment was classified as improved, stable or deteriorated
Moravan et al. 2009 Retrospective case review in the USA	7 people (mean age 47 years, 71% white) with biopsy-proven neurosarcoidosis that was refractory to corticosteroids (mean duration 8.5 months), who were treated with infliximab. 6 people also received mycophenolate mofetil	The dosage of infliximab was 5 mg/kg at weeks 0, 2, and 6, then every 6–8 weeks Mean duration of treatment 31 months No comparator	Response to treatment in terms of symptoms, and changes on MRI
Panselinas et al. 2009 Retrospective case review in the USA	14 people (mean age 43 years, 71% African-American) with sarcoidosis refractory to standard treatments (n=9) or with adverse effects on standard treatment (n=4) who had discontinued infliximab for at least 8 weeks. The reason for initiating infliximab was unknown for 1 person Neurosarcoidosis was the main treatment indication in 5 people (mean age 40 years, 100% African-American) 4/5 people were also taking corticosteroids, 1 in combination with cyclophosphamide	Infliximab 5 mg/kg at weeks 0, 2 and 6 then every 6 weeks For people with neurosarcoidosis, treatment duration ranged from 1 dose to 10.5 months. Mean follow-up after discontinuation of infliximab was 10.6 months No comparator	Sarcoidosis in the index organ was classified as resolved, improved, stable or deteriorated using objective measures (such as radiography)
Riancho-Zarrabeitia et al.	5 people (median age 55 years, ethnic origin not reported) with	The dosage of infliximab was	Response to treatment in terms

<p>2014 Retrospective case review in Spain</p>	<p>neurosarcoidosis (4 probable according to clinical, radiological and histological evidence, and 1 possible according to clinical presentation and exclusion of other diagnoses) treated with anti-TNFs 4/5 people were also taking methotrexate. All 5 were taking corticosteroids</p>	<p>5 mg/kg at weeks 0, 2, and 6, then every 6–8 weeks Mean follow-up on infliximab was 13 months No comparator</p>	<p>of symptoms, and changes on MRI</p>
<p>Russell et al. 2013 Retrospective case review in the US</p>	<p>26 people (mean age 51 years, 81% African American) with sarcoidosis refractory to corticosteroids or DMARDs or both, or who could not tolerate these treatments, who were using infliximab Previous ineffective treatments included corticosteroids (n=24), methotrexate (n=20) and hydroxychloroquine (n=23). More than half of cases were taking a corticosteroid and/or immunosuppressant when infliximab was started Neurosarcoidosis was the main treatment indication in 8 people</p>	<p>The average maximum infliximab dose was 511 mg (range 300–1000 mg) given on average every 5.5 weeks (range 4–6 weeks) Average treatment duration 46.2 months No comparator</p>	<p>Objective data (such as imaging, laboratory tests or clinician assessment) was used to grade clinical response to treatment as resolved, improved, unchanged or progressed</p>
<p>Schimmelpennink et al. 2018 Retrospective case review in the Netherlands</p>	<p>29 people (mean age 49.9 years, 79.3% white) with refractory sarcoidosis who received biosimilar infliximab because organ damage persisted on immunosuppressant treatment, or the immunosuppressant had to be discontinued because of toxicity. Sarcoidosis was diagnosed based on histological findings and exclusion of other diagnoses All 29 people used corticosteroids before infliximab was started, 23 used methotrexate, 6 used azathioprine, 7 used hydroxychloroquine, 4 used the original brand of infliximab, and 1 used adalimumab. Methotrexate or corticosteroids were used at a low dose with infliximab Neurosarcoidosis was the main treatment indication in 8 people</p>	<p>The dosage of infliximab was 5 mg/kg at weeks 0, 2, and then every 4 weeks Duration of treatment or follow-up is unclear, although some outcomes were assessed at 26 weeks No comparator</p>	<p>For neurosarcoidosis, organ function response was measure by assessing improvement of neurological symptoms or improvement of pain, and improvement of lesions seen on MRI</p>
<p>Abbreviations: DMARD, disease modifying antirheumatic drug; ePOST, extrapulmonary physician organ severity tool (17 individual extrapulmonary organs are scored on a scale from 0 [not affected] to 6 [very severely affected] and a total score is calculated [0 to 102]); MRI, magnetic resonance imaging; TNF, tumour necrosis factor</p>			

Details of the excluded studies are listed in the section on [evidence selection](#).

4. Results

An overview of the results for clinical effectiveness, safety and tolerability from the main studies can be found in the [evidence summary table](#). The research questions for the evidence review and the key outcomes identified in the scope are discussed in this section.

Clinical effectiveness

This section considers whether infliximab is clinically effective when used to treat neurosarcoidosis, particularly disease that is refractory or progressive.

Findings on magnetic resonance imaging (MRI)

In 56 people with adequate MRI follow-up, Gelfand et al. found that 52% of people using infliximab (29/56) had complete remission of neurosarcoidosis on MRI, 30% (17/56) had partial improvement, 14% remained stable (8/56) and 4% (2/56) got worse. A favourable response on MRI (partial or complete improvement) was seen in 82% of people (46/56). The median duration of treatment was 1.5 years. No statistical analyses were reported.

Clinical response

In the study by Gelfand et al., in terms of signs and symptoms of neurosarcoidosis after treatment with infliximab, 29% of people (19/66) recovered completely, 48% (32/66) partially improved but had some residual neurological disability, 18% (12/66) remained stable and 3% (2/66) got worse. A favourable response was seen in 80% of people (45/56) who had evaluations for both clinical response and MRI findings. No statistical analyses were reported.

Gelfand et al. found that the odds of a favourable treatment response were lower in people who had had neurosarcoidosis for a longer time when infliximab was started (adjusted [odds ratio](#) [OR] 0.79, 95% [confidence interval](#) [CI] 0.64 to 0.97, p=0.02). Combination treatment with infliximab plus another immunosuppressant was associated with higher odds of a favourable treatment response (adjusted OR 6.9, 95% CI 1.2 to 41.3, p=0.03). No association was found between infliximab treatment response and age, sex, race or exposure to prior immunosuppression.

Relapse

Gelfand et al. found that neurosarcoidosis recurred in 56% of people (9/16) who had experienced remission on infliximab, a mean of 5.7 months after treatment was stopped. No statistical analyses were reported.

ePOST scores

In the study by Jamilloux et al., the average [ePOST](#) CNS organ severity score decreased from 3.78 to 2.62 after treatment with an anti-TNF (usually infliximab) in 63 people with neurosarcoidosis. This improvement (1.16 on a 6-point scale) is [statistically significant](#) (p=0.001) but it is unclear if it is [clinically important](#).

Safety and tolerability

This section considers whether infliximab is safe when used to treat neurosarcoidosis, particularly disease that is refractory or progressive.

Observational studies

In the study by Gelfand et al., 7/66 people (11%) had infections that the investigators considered possibly related to infliximab treatment or the cumulative immunosuppressant treatments. One person discontinued infliximab because of myositis, which was considered to be medication-related.

In the study by Jamilloux et al., adverse events were not reported for the subgroup of people with neurosarcoidosis using infliximab. Of the 132 people in the study with sarcoidosis, 69 (52.3%) experienced 130 adverse events. Of these people, 31 had to stop treatment. The 130 adverse events included 90 infections (including pneumonia, urinary tract infections and bacterial sepsis) in 47 people, 25 of whom needed hospitalisation or treatment interruption.

No deaths occurred during the study by Gelfand et al. In Jamilloux et al., 3 people died but their deaths were not considered to be related to infliximab.

Adverse effects seen with infliximab in the observational studies included in this evidence summary appear to be consistent with those listed in the summary of product characteristics.

Summary of product characteristics

In clinical trials of infliximab for the licensed indications, upper respiratory tract infection was the most common adverse drug reaction, occurring in 25.3% of infliximab-treated people compared with 16.5% of controls. Other very common adverse effects (occurring in 1 in 10 people or more) include viral infections (such as influenza and herpes virus infection), headache, sinusitis, abdominal pain, nausea, generalised pain and infusion-related reactions.

The most serious adverse drug reactions associated with the use of TNF-alpha inhibitors that have been reported with infliximab include hepatitis B virus reactivation, congestive heart failure, serious infections (including sepsis, opportunistic infections and tuberculosis) and serious infusion reactions. Sarcoidosis and sarcoid-like reactions have been reported rarely.

See the [summaries of product characteristics](#) for complete lists of adverse effects for all of the available versions of infliximab. This information is taken from the summary of product characteristics for the originator infliximab product, [Remicade](#), but will also apply to the biosimilar infliximab products.

Infliximab is contraindicated in people with tuberculosis or other severe infections, and people with moderate or severe heart failure (NYHA class III/IV). In 2014, the [Drug Safety Update](#) from the MHRA advised that all people should be assessed for active and latent tuberculosis before starting treatment with a TNF-alpha inhibitor.

People must be monitored closely for infections including tuberculosis before, during and 6 months after treatment with infliximab. Caution should be used when considering the use

of infliximab in people with chronic infection or in those with a history of recurrent infections, including concomitant immunosuppressive therapy. Caution is also advised in people with hepatitis B virus infection and mild heart failure.

Results from small retrospective case reviews

The results of the small observational studies are included to give an indication of the broader volume of evidence for using infliximab for neurosarcoidosis. The results of these small studies are consistent with the larger studies in terms of clinical efficacy and safety. See table 2 for more details.

Table 2 Results from small retrospective case reviews

Study design	Efficacy	Adverse events
Hostettler et al. 2011 Retrospective case review in Switzerland (16 people with sarcoidosis who took infliximab for at least 12 months, main indication neurosarcoidosis in 6 people)	Of 6 people with neurosarcoidosis who took infliximab, 3 (50%) experienced complete remission, 2 (33%) experienced partial remission and 1 (17%) experienced no response (definitions of response were not reported, mean duration 36 months)	15/16 people had no clinically relevant adverse effects with infliximab over a mean of 29 months. After tolerating treatment for 4 years, 1 person had bradycardia 6 hours after an infliximab infusion
Leonhard et al. 2016 Retrospective case review in the Netherlands (52 people with neurosarcoidosis, 8 used infliximab and 1 used adalimumab)	Neurosarcoidosis improved in 4/9 people (44%) and stabilised in 5/9 people (56%) using anti-TNF therapy (mean follow-up 42 months) Treatment was successful and could be discontinued 1 person. In 2 people, treatment was discontinued because it failed to establish improvement and the other people were still receiving treatment at the last follow-up consultation	One person on prednisone, methotrexate and infliximab developed recurrent urinary tract infections. No other opportunistic infections were identified that could be attributed to anti-TNF therapy
Moravan et al. 2009 Retrospective case review in the USA (7 people with neurosarcoidosis treated with infliximab [6 also received mycophenolate mofetil])	All 7 people (100%) reported a dramatic improvement in symptoms after 1–3 infusions of infliximab. Improvement was confirmed on MRI in all cases 2 people experienced recurrence of symptoms and MRI abnormalities when infliximab was stopped. Both were restarted on infliximab with a positive response and remain on that treatment. Treatment was continuous in the other 5 people (mean duration 31 months)	Combination therapy was reportedly well-tolerated with no leukopenia, liver dysfunction or injection reactions. 1 person experienced transient fatigue immediately following the third infusion, which did not recur. Another person developed shingles after the second infusion, which led to a 2-month break in treatment

<p>Panselinas et al. 2009 Retrospective case review in the US (14 people with sarcoidosis who took infliximab, main indication neurosarcoidosis in 5 people)</p>	<p>Over a mean follow-up of 10.6 months, neurosarcoidosis resolved with infliximab treatment in 1 person (20%), with brain MRI appearing normal. 3 people (60%) experienced improvement (mental status and brain MRI improved and diabetes insipidus resolved in the first, tremors decreased in the second, and mental status and hydrocephalus improved in the third). Another person with visual defects caused by neurosarcoidosis remained stable, although this person only received 1 dose of infliximab</p> <p>People who discontinued infliximab were followed for a mean of 12 months. Everyone with neurosarcoidosis relapsed 3 to 17 months after stopping infliximab</p>	<p>Adverse events were not reported</p>
<p>Riancho-Zarrabeitia et al. 2014 Retrospective case review in Spain (5 people with neurosarcoidosis initially treated with infliximab)</p>	<p>Clinical improvement and/or improvements on imaging were seen in all 5 people (100%, mean follow-up 13 months) 2 people using infliximab experienced relapse 4 and 18 months after treatment stopped (1 then switched to adalimumab because of recurrent UTIs) Of the other 3 people, 1 person remained on infliximab, 1 person remained on adalimumab (switched following pneumonia) and 1 person (who had switched to adalimumab because symptoms recurred and persisted) was lost to medical follow-up</p>	<p>1 person had recurrent UTIs. 1 person had pneumonia. No infusion reactions were reported</p>
<p>Russell et al. 2013 Retrospective case review in the US (26 people with sarcoidosis who took infliximab, main indication neurosarcoidosis in 8 people)</p>	<p>Of 8 people with neurosarcoidosis treated with infliximab for, on average, 46.2 months, clinical resolution was seen in 3 (37%, sustained clinical improvement in disease activity was seen in 2 (25%) and no change was seen in 3 (37%, $p=0.03$ for resolution or improvement)</p>	<p>Over 46.2 months, adverse effects were seen in 15/26 people (58%), 3 of whom discontinued infliximab (due to severe pneumonia, positive tuberculosis skin test and recurrent sinusitis) Minor infection, rash and pneumonia were the most commonly reported adverse effects (n=4, n=4 and n=3 respectively)</p>
<p>Schimmelpennink et al. 2018 Retrospective case review in the Netherlands (29 people with sarcoidosis who took infliximab, main indication neurosarcoidosis in 8 people)</p>	<p>A functional response (improvement in symptoms or MRI findings) was seen in 3/8 people (37%) with neurosarcoidosis (mean duration of follow-up unclear)</p>	<p>Hospitalisation caused by infections occurred in 4/29 people (14%). No cases stopped treatment because of adverse events</p>
<p>Abbreviations: p, p value; MRI, magnetic resonance imaging; TNF, tumour necrosis factor; UTI, urinary tract infection</p>		

5. Discussion

Evidence strengths and limitations

The studies included in this evidence review are [observational studies](#), which are subject to [bias](#) and [confounding](#) and have many limitations affecting their application to clinical practice. They were retrospective [case series](#), which are subject to recall bias. Other limitations of case series include differences in the diagnosis, management and follow-up of individual cases, inconsistent and incomplete recorded data, loss to follow-up and, potentially, missed cases. Generally, the studies had no management protocols, no criteria for starting infliximab or measuring treatment outcomes, and no standardised assessment or structured follow-up.

The studies in the evidence summary were uncontrolled and, as is usual for rare diseases, had relatively small sample sizes. They were generally undertaken in specialist centres, which may have led to selection bias. Outcome assessment was not blinded in the studies and was generally undertaken by a single specialist clinician. Some of the outcomes assessed were subjective (for example, analysis of symptoms), but others were more objective (for example, MRI findings). The ePOST tool used to evaluate response to treatment in the study by Jamilloux et al. has not been validated for use in neurosarcoidosis.

In the study by Jamilloux et al. it is unclear what proportion of people with neurosarcoidosis were using infliximab rather than another anti-TNF (91% of 132 people in the study took infliximab, but only 63/132 people had neurosarcoidosis) and only ePOST scores were reported for the subgroup of people who were treated with an anti-TNF, not outcomes such as clinical response.

No evidence was found to determine whether or not infliximab is a cost-effective treatment option for neurosarcoidosis (particularly disease that is refractory or progressive).

Other treatments

No other treatments are generally considered at the same stage in the treatment pathway for refractory or progressive neurosarcoidosis as infliximab, although other anti-TNF treatments such as adalimumab and etanercept have been used. It is not known how infliximab compares with other anti-TNF treatments in terms of efficacy and safety.

6. Conclusion

The studies included in this evidence review suggest that infliximab can improve outcomes for some people with refractory or progressive neurosarcoidosis, with many reported as experiencing a complete or partial response. However, some people had residual symptoms and functional impairment after treatment, or experienced no response to treatment. Also, adverse effects of infliximab were sometimes serious and led to hospitalisation or discontinuation of treatment.

The optimal treatment regimen for infliximab for neurosarcoidosis is unclear because treatment regimens varied within and between the studies. The dosage of infliximab typically used was 3 to 7 mg/kg at weeks 0, 2, and 6, then every 6 to 8 weeks. The median duration of treatment in the key studies was between about 1.5 years and 1.7 years. Relapse of

neurosarcoidosis appeared to be common on stopping. Most people in the studies took corticosteroids and/or immunosuppressants in combination with infliximab, and it is unclear how this affects outcomes. It is also unclear what potential factors predict a good response to infliximab treatment.

The studies were undertaken in people with refractory or progressive neurosarcoidosis for whom corticosteroids and other treatments had proven ineffective, or who could not tolerate these treatments. Therefore, the results cannot be generalised to people with stable disease or those who have not tried standard treatments. Although the studies are relevant to the UK population overall, 2 small case series mainly included people of African-American ethnic origin ([Panselinas et al. 2009](#) and [Russell et al. 2013](#)). Sarcoidosis has been shown to be more severe and difficult to treat in this population but many cases in these studies experienced what was considered to be a good response to infliximab.

7. Evidence summary table

Use of infliximab to treat neurosarcoidosis							
Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
Study reference 1: Gelfand et al. 2017							
P1, retrospective non-comparative observational study	<p>6 centres in the USA</p> <p>66 people (mean age 45 years, 62% white) with probable (n=39, 59%) or confirmed (n=27, 41%) neurosarcoidosis who had been treated with infliximab</p> <p>Definite neurosarcoidosis was defined as biopsy consistent with sarcoidosis and a neurologic syndrome consistent with granulomatous inflammation. Probable neurosarcoidosis was defined as biopsy-confirmed sarcoidosis in an organ outside the nervous system and a neurologic syndrome consistent with granulomatous inflammation. Other potential diagnoses were also excluded</p> <p>31 people (47%) had myelitis or radiculomyelitis, 30 people had meningitis (45%), 17 people (26%) had pituitary or hypothalamic involvement and</p>	<p>Infliximab loading doses were typically given at weeks 0, 2 and 6</p> <p>Maintenance dosages were 3–7 mg/kg (most commonly 5 mg/kg) 4–8 weekly</p> <p>Median length of treatment 1.5 years</p> <p>No comparator</p>	Primary Clinical effectiveness	<p>Imaging response: stability, improvement or worsening of findings on MRI at last follow-up</p> <p>A favourable response was defined as partial or complete improvement on MRI</p>	<p>Of 56 people with adequate MRI follow-up, 29 people (51.8%) had complete remission, 17 people (30.1%) had partial improvement, 8 people (14.3%) saw no change and 2 people (3.6%) deteriorated</p> <p>A favourable response on MRI was seen in 46 people (82.1%) with adequate MRI follow-up</p> <p>No statistical analyses were reported</p>	6/10	<p>The research questions are stated but, as the study is an observational study it is insufficient to reliably answer the questions, and the results can only be considered hypothesis generating and cannot support any definitive conclusions. The methods are described and the results are generalisable to the population considered in the evidence review</p>
			Primary Clinical effectiveness	<p>Clinical response: stability, improvement, or worsening of neurologic symptoms and signs at last follow-up, assessed by the treating clinicians and chart review</p> <p>A favourable response was</p>	<p>Of 66 people in the study, 19 people (28.8%) had complete recovery, 32 people (48.5%) had partial improvement with some residual neurological disability, 12 people (18.2%) remained stable and 2 people (3.0%) deteriorated</p> <p>In 56 people with sufficient information for combined clinical and imaging evaluation, a favourable response was seen in 45 people (80.4%)</p> <p>No statistical analyses are reported</p>		

Use of infliximab to treat neurosarcoidosis

Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
	<p>16 people (24%) had optic neuropathy</p> <p>65 people (98%) had previously been treated with glucocorticoids. When infliximab was started, 52 people (79%) were taking glucocorticoids</p> <p>52 people (79%) previously took at least 1 immunosuppressant. When infliximab was started, 52 people (79%) were taking an immunosuppressant, usually methotrexate (n=22, 33%), mycophenolate mofetil (n=18, 27%) or azathioprine (n=10, 15%)</p>			<p>defined as partial or complete improvement on MRI together with clinical stability, partial clinical improvement or complete clinical recovery</p>	<p>The longer neurosarcoidosis had been present before infliximab initiation, the lower the odds of a favourable treatment response (adjusted OR 0.79, 95% CI 0.64 to 0.97, p=0.02)</p> <p>Combination therapy of infliximab with another immunosuppressant was associated with higher odds of a favourable treatment response (adjusted OR 6.9, 95% CI 1.2 to 41.3, p=0.03)</p> <p>No association was found between infliximab treatment response and age, sex, race, or exposure to prior immunosuppression</p>		
			Secondary Clinical effectiveness	Recurrence of neurosarcoidosis after discontinuing infliximab	<p>Of 16 people who experienced remission of neurosarcoidosis with infliximab, the disease recurred in 9 people (56%) within a mean of 5.7 months following infliximab discontinuation (in the same location in 60%)</p> <p>No statistical analyses are reported</p>		
			Secondary Safety	Infections	7 people (10.6%) had infections that the investigators considered possibly related to infliximab treatment or the cumulative immunosuppressant treatments		
			Secondary Safety	Treatment discontinuation	1 person discontinued infliximab because of myositis, which was considered to be medication-related		

Use of infliximab to treat neurosarcoidosis							
Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
			Secondary Safety	Death	No deaths occurred during the study period		
<p>Critical appraisal summary: This is a retrospective non-comparative observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. Infliximab treatment protocols were not standardised within or across the 6 centres, and variability in infusion protocols and use of concurrent immunotherapies could have had some influence on efficacy and safety. Infliximab was most commonly used as combination therapy, rather than monotherapy, and some of the treatment benefit could relate to synergistic effects of combination immunosuppression. Clinical and imaging follow-up was not standardised</p> <p>The authors concluded that most people with neurosarcoidosis treated with infliximab exhibit favourable imaging and clinical treatment responses, including some previously refractory to other immunosuppressive treatments. However, the condition returned in more than half of people who had previously been in remission while undergoing infliximab treatment</p>							
<p>Study reference 2: Jamilloux et al. 2017</p>							
P1, retrospective non-comparative observational study	25 centres in France 132 people (median age 45 years, 45% white) with refractory sarcoidosis who had used an anti-TNF medicine. Infliximab was the first-line anti-TNF in 120 people (91%). Others included adalimumab, etanercept and certolizumab Sarcoidosis was diagnosed according to WASOG guidelines, and considered refractory when it was not controlled despite previous use of at least 1 immunosuppressant (mean 1.6 immunosuppressants)	When infliximab was used, it was given at a dosage of 3–5 mg/kg at weeks 0, 2, and 6, then every 4–8 weeks Median follow-up 20.5 months No comparator	Primary Clinical effectiveness	Change in ePOST scores	In the 63 people with neurosarcoidosis, the ePOST CNS organ score at baseline was 3.78/6. Following anti-TNF treatment (usually infliximab), the score was 2.62, a statistically significant improvement (p=0.001). It is unclear if this change is clinically important	6/10 The research questions are stated but, as the study is an observational study it is insufficient to reliably answer the questions, and the results can only be considered hypothesis generating and cannot support any definitive conclusions. The	Direct study focusing on people with the indication and characteristics of interest
			Secondary Safety	Adverse events requiring treatment discontinuation	Adverse events were not reported for the subgroup of people with neurosarcoidosis Of the 132 people in the study, 69 (52.3%) experienced 130 adverse events that required treatment discontinuation		
			Secondary Safety	Infections	In 132 people, 90 infections (including pneumonia, urinary tract infections, bacterial sepsis) occurred in 47 people (35.6%). 25 of these required		

Use of infliximab to treat neurosarcoidosis

Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
	<p>Before anti-TNF initiation, 128 people (97%) had received corticosteroids and 125 people (95%) had received at least 1 immunosuppressant over a median duration of 16 months</p> <p>During anti-TNF treatment, 113 people (86%) received corticosteroids and 97 people (73%) received an immunosuppressant: methotrexate (n=81, 61%), azathioprine (n=10, 8%) or mycophenolate mofetil (n=6, 5%)</p> <p>63 people had neurosarcoidosis according to Zajicek's classification for neurosarcoidosis. It is unclear how many people with neurosarcoidosis were using infliximab</p>		Secondary Safety	Death	<p>hospitalisation or treatment interruption</p> <p>3 people died but their deaths were not considered to be related to infliximab</p>	<p>methods are described and the results are generalisable to the population considered in the evidence review</p>	
<p>Critical appraisal summary: This is a retrospective non-comparative observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. Treatment protocols were not standardised within or across the 6 centres, and variability in infusion protocols and use of concurrent immunotherapies could have had some influence on efficacy and safety. Anti-TNF treatment was most commonly used as combination therapy, rather than monotherapy, and some of the treatment benefit could relate to synergistic effects of combination immunosuppression. Only ePOST scores are reported for the subgroup of people with neurosarcoidosis. Also, it is unclear what proportion of people with neurosarcoidosis used infliximab rather than another anti-TNF. Similarly, safety outcomes relate to all anti-TNFs, not just infliximab. 91% of people in the study used infliximab.</p> <p>The authors concluded that anti-TNF therapy is effective in neurosarcoidosis. However, the rate of adverse events is high</p>							

Use of infliximab to treat neurosarcoidosis							
Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability
Abbreviations: CI, confidence interval ; ePOST, extrapulmonary physician organ severity tool (17 extrapulmonary organs are scored on a scale from 0 [not affected] to 6 [very severely affected] and a total score is calculated [0 to 102]); MRI, magnetic resonance imaging; OR, odds ratio ; WASOG, World Association of Sarcoidosis and other Granulomatous disorders							

8. Grade of evidence table

Use of infliximab to treat neurosarcoidosis					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Response to treatment on MRI magnetic resonance imaging (MRI)	Gelfand et al. 2017	6/10	Direct study	C	<p>This outcome looked at whether images of people's brain (obtained using a procedure called MRI) showed that the disease improved, stayed the same or got worse when they were using infliximab.</p> <p>The study found that, in people using infliximab for 1.5 years on average, neurosarcoidosis resolved completely in 52% (29/56), partially improved in 30% (17/56), stayed the same in 14% (8/56) and got worse in 4% (2/56). A favourable response on MRI (partial or complete improvement) was seen in 82% of people (46/56).</p> <p>This suggests that neurosarcoidosis resolved in the brain in more than half of people using infliximab, and 8 out of 10 people experienced some improvement.</p> <p>These results should be interpreted with caution because the study is small, uncontrolled and retrospective. Weaknesses in the study's design and</p>

					conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions.
Clinical response to treatment	Gelfand et al. 2017	6/10	Direct study	C	<p>This outcome looked at how many people's signs and symptoms of neurosarcoidosis improved, stayed the same or got worse, in the opinion of their specialist, when the neurosarcoidosis was treated with infliximab.</p> <p>When people were assessed by their specialist after using infliximab, the study found that clinical signs and symptoms of neurosarcoidosis resolved completely in 29% (19/66), partially improved in 48% (32/66), stayed the same in 18% (12/66) and got worse in 3% (2/66). A favourable response with complete or partial recovery was seen in 80% of people (45/56) who had evaluations for both clinical response and MRI findings.</p> <p>This suggests that clinical signs and symptoms of neurosarcoidosis resolved in just under a third of people using infliximab, and 8 out of 10 people experienced some improvement in both findings on MRI and clinical signs and symptoms.</p> <p>These results should be interpreted with caution because the study is small, uncontrolled and retrospective. Weaknesses in the study's design and conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions.</p>
Odds of a favourable response to treatment based on duration of disease	Gelfand et al. 2017	6/10	Direct study	C	<p>This outcome looked at whether the chances of people's signs and symptoms of neurosarcoidosis improving or resolving when they were treated with infliximab was affected by how long they had had the disease.</p> <p>The study found that the odds of a favourable treatment response were lower in people who had had neurosarcoidosis for a longer time when infliximab</p>

					<p>was started (adjusted odds ratio 0.79, p=0.02).</p> <p>This suggests that the odds of responding to infliximab were better in people who had had the disease for a shorter period of time. However, the time periods that were compared were not specified in the paper.</p> <p>These results should be interpreted with caution because the study is small, uncontrolled and retrospective. Weaknesses in the study's design and conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions.</p>
Relapse	Gelfand et al. 2017	6/10	Direct study	C	<p>This outcome looks at the number of people whose signs and symptoms of neurosarcoidosis came back after they stopped using infliximab.</p> <p>Gelfand et al. found that neurosarcoidosis recurred in 56% of people (9/16) who had experienced remission after using infliximab for, on average, 1.5 years. Relapse occurred, on average, about 6 months after treatment was stopped.</p> <p>These results suggest that around half of people with neurosarcoidosis experience relapse when they have been treated with infliximab for about 1.5 years.</p> <p>These results should be interpreted with caution because the study is small, uncontrolled and retrospective. Weaknesses in the study's design and conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions.</p>
Changes in ePOST scores	Jamilloux et al. 2017	6/10	Direct study	C	<p>This outcome looks at the change in scores obtained using the extrapulmonary physician organ severity tool (ePOST) before and after treatment with infliximab. For the full ePOST score, 17 individual organs (apart from the lungs) are scored on a scale from 0 (meaning not affected) to 6 (meaning very severely affected)</p>

					<p>and a total score is calculated (0 to 102). For this outcome, just the central nervous system (CNS) organ score is used because this is most relevant in neurosarcoidosis, and the score can range from 0 to 6.</p> <p>In the study by Jamilloux et al., the average ePOST CNS organ severity score changed from 3.78 to 2.62 after treatment with an anti-TNF (usually infliximab) in 63 people with neurosarcoidosis. This improvement is statistically significant ($p=0.001$) but it is unclear if it is clinically important.</p> <p>This shows that people's score improved by 1.16 on a 6-point scale, which suggests that, on average, their neurosarcoidosis improved. However, although individual people may feel quite a large benefit, others may experience no benefit, and it is unclear if a 1 point improvement is large enough to be important to the overall population with neurosarcoidosis.</p> <p>These results should be interpreted with caution because the study is small, uncontrolled and retrospective. Weaknesses in the study's design and conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions.</p>
Adverse effects	Gelfand et al. 2017	6/10	Direct study	C	<p>This outcome looks at how many people had side effects while they were using infliximab for neurosarcoidosis.</p> <p>In the study by Gelfand et al., 7/66 people (11%) had infections that the investigators considered possibly related to infliximab treatment or the combination of treatments they were taking to suppress their immune system. One person stopped using infliximab because of myositis (inflammation of the muscle), which was considered to be medication-related.</p> <p>The results suggest that, when infliximab is used for</p>

					<p>neurosarcoidosis, the adverse effects seen are similar to those that are seen when it is used for its licensed indications, as listed in the summary of product characteristics; for example, infections are common.</p> <p>These results should be interpreted with caution because the study is small, uncontrolled and retrospective. Weaknesses in the study's design and conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions.</p>
Deaths	Gelfand et al. 2017	6/10	Direct study	B	<p>This outcome looks at how many people died while they were using infliximab for neurosarcoidosis.</p> <p>No deaths occurred during the study by Gelfand et al. In Jamilloux et al., 3 people died but their deaths were not considered to be related to infliximab.</p> <p>This suggests that death is rare in people using infliximab for neurosarcoidosis.</p> <p>These results should be interpreted with caution because the studies are small, uncontrolled, and did not use standardised treatment and monitoring protocols. Weaknesses in the studies' design and conduct mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions.</p>
	Jamilloux et al. 2017	6/10	Direct study		

9. Literature search terms

Search strategy	
<p>P – Patients/ Population</p> <p>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?</p>	<p>Patients with neurosarcoidosis (CNS sarcoidosis) that is:</p> <ul style="list-style-type: none"> • Refractory to current treatments (e.g. corticosteroids and immunosuppression) OR • Progressive despite current treatments
<p>I – Intervention</p> <p>Which intervention, treatment or approach should be used?</p>	<p>Use of infliximab alone or as an adjuvant to current standard pharmaceutical treatments (e.g. corticosteroids and immunosuppression)</p>
<p>C – Comparison</p> <p>What is/are the main alternative/s to compare with the intervention being considered?</p>	<p>Any treatments that do not include infliximab</p>
<p>O – Outcomes</p> <p>What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission</p>	<p><u>Critical to decision-making: zinc salts as an alternative to trientine and penicillamine</u></p> <ol style="list-style-type: none"> 1. Survival 2. Disease progression <ul style="list-style-type: none"> • Changes on MRI of the CNS • Reduction in corticosteroid usage • Improvement in neurological function (using validated scores if possible, for example the modified Rankin Scale) <p><u>Important to decision-making:</u></p> <ol style="list-style-type: none"> 3. Quality of life 4. Adverse events 5. Cost effectiveness

Assumptions / limits applied to search

Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc.

- Publication type
Peer-reviewed articles published in journals. Conference abstracts, grey literature, anecdotal and unpublished evidence should be excluded.
- Language
Articles published in the English language.
- Time frame
Articles published in the last 10 years.
- Study design
Controlled studies, uncontrolled studies, and case studies or case series of any size

10. Search strategy

Database search strategies

Database: Medline

Platform: Ovid

Version: Ovid MEDLINE(R) ALL 1946 to May 25, 2018

Search date: 29th May 2018

Number of results retrieved: 61

Search strategy:

Database: Ovid MEDLINE(R) ALL <1946 to May 25, 2018>

-
- 1 exp Sarcoidosis/ (23718)
 - 2 Sarcoidosis.tw. (22146)
 - 3 1 or 2 (28443)
 - 4 neuro*.tw. (1604441)
 - 5 (cns or central nervous system).tw. (210516)
 - 6 4 or 5 (1713390)
 - 7 3 and 6 (1864)
 - 8 (neurosarcoidosis or neuro-sarcoidosis or "neuro sarcoidosis").tw. (888)
 - 9 7 or 8 (1969)
 - 10 Infliximab/ (8989)
 - 11 (infliximab or remicade or flixabi or inflectra or remsima).tw. (10499)
 - 12 10 or 11 (12742)
 - 13 9 and 12 (70)
 - 14 limit 13 to english language (61)

Database: Medline in-process

Platform: Ovid

Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 25, 2018>

Search date: 29th May 2018

Number of results retrieved: 12

Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 25, 2018>

-
- 1 exp Sarcoidosis/ (0)
 - 2 Sarcoidosis.tw. (1538)
 - 3 1 or 2 (1538)
 - 4 neuro*.tw. (138711)
 - 5 (cns or central nervous system).tw. (15306)
 - 6 4 or 5 (145998)
 - 7 3 and 6 (138)
 - 8 (neurosarcoidosis or neuro-sarcoidosis or "neuro sarcoidosis").tw. (94)
 - 9 7 or 8 (180)

- 10 Infiximab/ (0)
- 11 (infiximab or remicade or flixabi or inflectra or remsima).tw. (1247)
- 12 10 or 11 (1247)
- 13 9 and 12 (12)
- 14 limit 13 to english language (12)

Database: Medline epubs ahead of print

Platform: Ovid

Version: Ovid MEDLINE(R) Epub Ahead of Print <May 25, 2018>

Search date: 29th May 2018

Number of results retrieved: 1

Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <May 25, 2018>

Search Strategy:

-
- 1 exp Sarcoidosis/ (0)
 - 2 Sarcoidosis.tw. (195)
 - 3 1 or 2 (195)
 - 4 neuro*.tw. (25910)
 - 5 (cns or central nervous system).tw. (3065)
 - 6 4 or 5 (27282)
 - 7 3 and 6 (17)
 - 8 (neurosarcoidosis or neuro-sarcoidosis or "neuro sarcoidosis").tw. (11)
 - 9 7 or 8 (25)
 - 10 Infiximab/ (0)
 - 11 (infiximab or remicade or flixabi or inflectra or remsima).tw. (217)
 - 12 10 or 11 (217)
 - 13 9 and 12 (2)
 - 14 limit 13 to english language (1)

Database: Medline daily update

Platform: Ovid

Version: Ovid MEDLINE(R) Daily Update <May 25, 2018>

Search date: 29th May 2018

Number of results retrieved: 0

Search strategy

Database: Ovid MEDLINE(R) Daily Update <May 25, 2018>

-
- 1 exp Sarcoidosis/ (8)
 - 2 Sarcoidosis.tw. (9)
 - 3 1 or 2 (9)
 - 4 neuro*.tw. (1571)
 - 5 (cns or central nervous system).tw. (148)
 - 6 4 or 5 (1634)
 - 7 3 and 6 (0)
 - 8 (neurosarcoidosis or neuro-sarcoidosis or "neuro sarcoidosis").tw. (0)
 - 9 7 or 8 (0)

- 10 Infiximab/ (16)
- 11 (infiximab or remicade or flixabi or inflectra or remsima).tw. . (17)
- 12 10 or 11 (19)
- 13 9 and 12 (0)
- 14 limit 13 to english language (0)

Database: Embase

Platform: Ovid

Version: Embase <1974 to 2018 Week 22>

Search date: 29th May 2018

Number of results retrieved: 147

Database: Embase <1974 to 2018 Week 22>

-
- 1 exp sarcoidosis/ (34370)
 - 2 Sarcoidosis.tw. (29144)
 - 3 1 or 2 (39247)
 - 4 neuro*.tw. (2113461)
 - 5 (cns or central nervous system).tw. (276997)
 - 6 4 or 5 (2254407)
 - 7 3 and 6 (3362)
 - 8 neurosarcoidosis/ (172)
 - 9 neurosarcoidosis.tw. (1288)
 - 10 8 or 9 (1336)
 - 11 7 or 10 (3424)
 - 12 infiximab/ (43466)
 - 13 (infiximab or remicade or flixabi or inflectra or remsima).tw. (24632)
 - 14 12 or 13 (44165)
 - 15 11 and 14 (229)
 - 16 limit 15 to english language (218)
 - 17 limit 16 to (conference abstract or conference paper or "conference review" or letter or note) (71)
 - 18 16 not 17 (147)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED

Platform: Wiley

Version:

CDSR – Issue 5 of 12, May 2018

DARE – 2 of 4, April 2015 (legacy database)

CENTRAL – Issue 4 of 12, April 2018

HTA – 4 of 4, October 2016 (legacy database)

NHS EED – 2 of 4, April 2015 (legacy database)

Search date: 29th May 2018

Number of results retrieved: CDSR – 0 ; DARE – 0 ; CENTRAL – 3; HTA – 1; NHS EED - 0.

Search strategy:

Date Run: 29/05/18 10:42:07.444

ID	Search	Hits
#1	MeSH descriptor: [Sarcoidosis] explode all trees	145
#2	Sarcoidosis:ti,ab,kw (Word variations have been searched)	430
#3	#1 or #2	430
#4	neuro*:ti,ab,kw (Word variations have been searched)	74399
#5	cns or "central nervous system":ti,ab,kw (Word variations have been searched)	9492
#6	#4 or #5	81173
#7	#3 and #6	27
#8	neurosarcoidosis or neuro-sarcoidosis or "neuro sarcoidosis":ti,ab,kw (Word variations have been searched)	7
#9	#7 or #8	28
#10	MeSH descriptor: [Infliximab] explode all trees	493
#11	infliximab or remicade or flixabi or inflectra or remsima:ti,ab,kw (Word variations have been searched)	1769
#12	#10 or #11	1769
#13	#9 and #12	4

Additional search for sarcoidosis 2016+ (run on 6th June 18)
(‘NOT’ was used to remove results already found from the strategies above)
Database: Ovid MEDLINE(R) ALL

- 1 exp Sarcoidosis/
- 2 Sarcoidosis.tw.
- 3 1 or 2
- 4 neuro*.tw.
- 5 (cns or central nervous system).tw.
- 6 4 or 5
- 7 3 and 6
- 8 (neurosarcoidosis or neuro-sarcoidosis or "neuro sarcoidosis").tw.
- 9 7 or 8
- 10 Infliximab/
- 11 (infliximab or remicade or flixabi or inflectra or remsima).tw.
- 12 10 or 11
- 13 9 and 12
- 14 3 and 12
- 15 limit 14 to ed=20160901-20180606
- 16 13 or 15
- 17 limit 16 to english language

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 18, 2018>

Search Strategy:

- 1 exp Sarcoidosis/
- 2 Sarcoidosis.tw.
- 3 1 or 2

- 4 neuro*.tw.
- 5 (cns or central nervous system).tw.
- 6 4 or 5
- 7 3 and 6
- 8 (neurosarcoidosis or neuro-sarcoidosis or "neuro sarcoidosis").tw.
- 9 7 or 8
- 10 Infliximab/
- 11 (infliximab or remicade or flixabi or inflectra or remsima).tw.
- 12 10 or 11
- 13 9 and 12
- 14 3 and 12
- 15 limit 14 to yr="2016 -Current"
- 16 13 or 15
- 17 limit 16 to english language

Database: Ovid MEDLINE(R) Epub Ahead of Print

- 1 exp Sarcoidosis/
- 2 Sarcoidosis.tw.
- 3 1 or 2
- 4 neuro*.tw.
- 5 (cns or central nervous system).tw.
- 6 4 or 5
- 7 3 and 6
- 8 (neurosarcoidosis or neuro-sarcoidosis or "neuro sarcoidosis").tw.
- 9 7 or 8
- 10 Infliximab/
- 11 (infliximab or remicade or flixabi or inflectra or remsima).tw.
- 12 10 or 11
- 13 9 and 12
- 14 3 and 12
- 15 limit 14 to yr="2016 -Current"
- 16 13 or 15
- 17 limit 16 to english language

Database: Ovid MEDLINE(R) Daily Update

- 1 exp Sarcoidosis/
- 2 Sarcoidosis.tw.
- 3 1 or 2
- 4 neuro*.tw.
- 5 (cns or central nervous system).tw.
- 6 4 or 5
- 7 3 and 6
- 8 (neurosarcoidosis or neuro-sarcoidosis or "neuro sarcoidosis").tw.
- 9 7 or 8
- 10 Infliximab/

- 11 (infliximab or remicade or flixabi or inflectra or remsima).tw.
- 12 10 or 11
- 13 9 and 12
- 14 3 and 12
- 15 limit 14 to yr="2016 -Current"
- 16 13 or 15
- 17 limit 16 to english language

Database: Embase

-
- 1 exp sarcoidosis/
 - 2 Sarcoidosis.tw.
 - 3 1 or 2
 - 4 neuro*.tw.
 - 5 (cns or central nervous system).tw.
 - 6 4 or 5
 - 7 3 and 6
 - 8 neurosarcoidosis/
 - 9 neurosarcoidosis.tw.
 - 10 8 or 9
 - 11 7 or 10
 - 12 infliximab/
 - 13 (infliximab or remicade or flixabi or inflectra or remsima).tw.
 - 14 12 or 13
 - 15 11 and 14
 - 16 3 and 14
 - 17 ("201609" or 2017* or 2018*).dc.
 - 18 16 and 17
 - 19 15 or 18
 - 20 limit 19 to english language
 - 21 limit 20 to (conference abstract or conference paper or "conference review")
 - 22 20 not 21

Cochrane Library - CENTRAL

- | ID | Search | Hits |
|-----|--|------|
| #1 | MeSH descriptor: [Sarcoidosis] explode all trees | |
| #2 | Sarcoidosis:ti,ab,kw (Word variations have been searched) | |
| #3 | #1 or #2 | |
| #4 | neuro*:ti,ab,kw (Word variations have been searched) | |
| #5 | cns or "central nervous system":ti,ab,kw (Word variations have been searched) | |
| #6 | #4 or #5 | |
| #7 | #3 and #6 | |
| #8 | neurosarcoidosis or neuro-sarcoidosis or "neuro sarcoidosis":ti,ab,kw (Word variations have been searched) | |
| #9 | #7 or #8 | |
| #10 | MeSH descriptor: [Infliximab] explode all trees | |
| #11 | infliximab or remicade or flixabi or inflectra or remsima:ti,ab,kw (Word variations have been searched) | |

#12 #10 or #11
#13 #9 and #12
#14 #3 and #12
#15 #14 Publication Year from 2016 to 2018
#16 #13 or #15

11. Evidence selection

A literature search was conducted which identified 234 references (see [search strategy](#) for full details). These references were screened using their titles and abstracts and 16 full text references were obtained and assessed for relevance. Of these, 5 references are included in the evidence summary. The remaining 11 references were excluded and are listed in the following table.

On checking the evidence identified for a previous [NICE evidence summary on infliximab for refractory extrapulmonary sarcoidosis](#) in 2016, 6 other papers on mixed manifestations of sarcoidosis were identified that presented results separately for people with neurological sarcoidosis. On investigation it was found that these papers had not been coded for neurosarcoidosis and, therefore, were not identified in the search. Of the 6 papers, 3 were included in the evidence summary and 3 were excluded and listed in the following table.

A further search was undertaken using broader search terms, looking for additional papers on infliximab for refractory sarcoidosis published since the search for the previous evidence summary was undertaken (see [search strategy](#) for full details). The 23 additional references identified were screened using their titles and abstracts. One full text reference was obtained and assessed for relevance, and subsequently included in the evidence summary.

A total of 9 references were included in the evidence summary.

Reasons for exclusion are:

- Single case reports or case series containing fewer than 5 people with neurosarcoidosis using infliximab
- Outcomes not reported for the subgroup of people with neurosarcoidosis using infliximab
- Cases probably included in a larger study
- Narrative reviews
- Letters
- Abstract only

Study reference	Reason for exclusion
Aguiar M, Marcal N, Mendes AC, et al. (2011) Infliximab for treating sarcoidosis patients, Portuguese experience. <i>Revista portuguesa de pneumologia</i> 17: 85–93	3 cases with neurosarcoidosis only
Chapelon-Abric C, Saadoun D, Biard L, et al. (2015) Long-term outcome of infliximab in severe chronic and refractory systemic sarcoidosis: a report of 16 cases. <i>Clinical and Experimental Rheumatology</i> 33(4): 509–15	Cases likely to be included in Jamilloux et al. 2017
Cohen Aubart F, Bouvry D, Galanaud D, et al. (2017) Long-term outcomes of refractory neurosarcoidosis treated with infliximab. <i>Journal of Neurology</i> 264(5): 891–7	Cases likely to be included in Jamilloux et al. 2017
Corbett James (2009) Treating CNS sarcoidosis with infliximab and mycophenolate mofetil. <i>Current Neurology and Neuroscience Reports</i> 9(5): 339–40	Review of study by Moravan et al. 2009
Joubert B, Chapelon-Abric C, Biard L, et al. (2017) Association of prognostic factors and immunosuppressive treatment with long-term outcomes in neurosarcoidosis. <i>JAMA Neurology</i> 74(11): 1336–44	Cases likely to be included in Jamilloux et al. 2017
Koczman JJ, Rouleau J, Gaunt M, et al. (2008) Neuro-ophthalmic sarcoidosis: The University of Iowa experience. <i>Seminars in Ophthalmology</i> 23(3): 157–68	Single case report
Morcos Zeyad (2003) Refractory neurosarcoidosis responding to infliximab. <i>Neurology</i> 60(7): 1220–1	Letter
O'Connell K, Williams L, Jones J, et al. (2017) Neurosarcoidosis: clinical presentations and changing treatment patterns in an Irish Caucasian population. <i>Irish Journal of Medical Science</i> 186(3): 759–66	2 cases using infliximab only
Pereira J, Anderson NE, Mcauley, D et al. (2011) Medically refractory neurosarcoidosis treated with infliximab. <i>Internal Medicine Journal</i> 41(4): 354–7	3 cases only
Santos E, Shaunak S, Renowden S, et al. (2010) Treatment of refractory neurosarcoidosis with infliximab. <i>Journal of neurology, neurosurgery, and psychiatry</i> 81(3): 241–6	4 cases only
Sodhi M, Pearson K, White ES, et al. (2009) Infliximab therapy rescues cyclophosphamide failure in severe central nervous system sarcoidosis. <i>Respiratory medicine</i> 103(2): 268–73	4 cases only
Van Rijswijk HNAJ, Vorselaars ADM, Ruven HJT et al. (2013) Changes in disease activity, lung function and quality of life in patients with refractory sarcoidosis after anti-TNF treatment. <i>Expert Opinion on Orphan Drugs</i> 1: 437–443	Outcomes for neurosarcoidosis and small fibre neuropathy reported together Cases likely to be included in Schimmelpennink et al. 2018
Sollberger M, Fluri F, Baumann T, et al. (2004) Successful treatment of steroid-refractory neurosarcoidosis with infliximab. <i>Journal of Neurology</i> 251(6): 760–1	Single case report
Vorselaars ADM, Crommelin HA, Deneer VHM et al. (2015) Effectiveness of infliximab in refractory FDG PET-positive sarcoidosis. <i>European Respiratory Journal</i> 46: 175–85	Outcomes not reported for 3 people with neurosarcoidosis

12. Related NICE guidance and NHS England clinical policies

NHS England and NICE have not issued any guidelines or policies on managing neurosarcoidosis with infliximab. NICE has previously published 2 evidence summaries on infliximab for sarcoidosis: [Refractory extrapulmonary sarcoidosis: infliximab](#) (2016) and [Pulmonary sarcoidosis: infliximab](#) (2016).

13. Terms used in this evidence summary

Abbreviations

Term	Definition
CNS	Central nervous system
ePOST	Extrapulmonary physician organ severity tool
MRI	Magnetic resonance imaging
TNF	Tumour necrosis factor

Medical definitions

Term	Definition
Anti-TNF	A medicine that stops tumour necrosis factors being produced, thereby reducing inflammation and disease activity
Central nervous system (CNS)	The brain and spinal cord
Cranial nerves	A group of 12 nerves to the head and neck
Extrapulmonary physician organ severity tool (ePOST)	A tool looking at the severity of sarcoidosis in 17 organs (apart from the lungs) using all clinical information available (including laboratory analyses and clinical assessments). Each organ is scored on a scale from 0 (not affected) to 6 (very severely affected). Therefore, the ePOST score ranges from 0 to 102
Granulomas	Lumps caused by clusters of inflammatory cells
Meningitis	Inflammation of the lining of the brain and spinal cord
Neurosarcoidosis	Sarcoidosis affecting the CNS
Peripheral nervous system	The nerves to the body and the cranial nerves
Tumour necrosis factor (TNF)	A cell signalling protein or cytokine which is involved in inflammation in the body
Vasculitis	Inflammation of the blood vessels

14. References

Chapelon-Abric C, Saadoun D, Biard L et al. (2015) [Long-term outcome of infliximab in severe chronic and refractory systemic sarcoidosis: a report of 16 cases](#) Clinical and Experimental Rheumatology 33: 509–15

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- Hostettler KE, Studler U, Tamm M et al. (2012) [Long-term treatment with infliximab in patients with sarcoidosis](#). Respiration 83: 218–24
- Jamilloux Y, Cohen-Aubart F, Chapelon-Abric C, et al. (2017) [Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: A multicenter study of 132 patients](#). Seminars in Arthritis and Rheumatism 47(2), 288–94
- Joubert B, Chapelon-Abric C, Biard L, et al. (2017) [Association of prognostic factors and immunosuppressive treatment with long-term outcomes in neurosarcoidosis](#). JAMA Neurology 74(11): 1336–44
- Leonhard SE, Fritz D, Eftimov F, et al. (2016) [Neurosarcoidosis in a tertiary referral center: a cross-sectional cohort study](#). Medicine 95(14): e3277
- Moravan M and Segal BM (2009) [Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil](#). Neurology 72(4), 337–40
- Panselinas E, Rodgers JK and Judson MA (2009) [Clinical outcomes in sarcoidosis after cessation of infliximab treatment](#). Respirology 14:522–8
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