Clinical Commissioning Policy:

Infliximab for refractory sarcoidosis (excluding neurosarcoidosis) (adults) [2204]

Summary

Infliximab is recommended to be available off-label as a routine commissioning treatment option for refractory sarcoidosis (excluding neurosarcoidosis) within the criteria set out in this document.

The policy is restricted to adults in line with the findings from the evidence review. Infliximab may be used in children aged six years and older via NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children). Note that infliximab is not licenced in adults for sarcoidosis and therefore this is an off-label use.

Committee discussion

Clinical Panel considered the evidence base and the recommendation was made to progress the policy as for routine commissioning. Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed on the NHS England website.

What we have decided

NHS England has carefully reviewed the evidence to treat refractory sarcoidosis (excluding neurosarcoidosis) with intravenous infliximab. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed on the NHS England website.

Links and updates to other policies

This document may be used in conjunction with 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children).

Plain language summary

About sarcoidosis (excluding neurosarcoidosis)

Sarcoidosis (also known as sarcoid) is a condition where cells in the body clump together to make small lumps called granulomas. If these develop in organs in the body, they can stop the organ working correctly. The disease can affect more than one organ system in a patient so there are several types of sarcoidosis. Sarcoidosis mainly affects the lungs (more than 90% of patients have lung involvement including both the lymph nodes and the lung tissue), skin and eyes. However, it can also affect other organs, including the heart, liver, and brain.

The cause of sarcoidosis is unknown and there is currently no cure for the condition. The symptoms of the disease vary and partially depend on the body part affected. General symptoms can include cough, breathlessness, red or painful eyes, swollen glands, rashes, muscle and joint pain or numbness in the face, arms, or legs. Patients may also feel tired, suffer from weight loss or experience fevers and night sweats. Some patients do not have any symptoms at all.

Most patients with sarcoidosis do not require treatment. However, around a third have more serious disease and require therapies such as steroids and drugs that suppress the immune system. The overall death rate (mortality) in sarcoidosis is 1-5% usually due to lung, heart or brain involvement and their associated complications.

Refractory disease is defined as sarcoid disease that has failed to respond to standard treatments (for example corticosteroids and/or at least one conventional Disease Modifying Anti Rheumatic Drug (cDMARD)) or the standard treatments are contraindicated.

About current treatment

First-line treatment is usually with oral corticosteroids such as prednisolone, with a maintenance dose for a period of 6-24 months. Steroid creams and eye drops may be effective if the inflammation is restricted to skin (cutaneous sarcoidosis). Other treatments that may be added if the disease does not respond, or if a steroid-sparing agent is needed (typically when patients also have diabetes mellitus and osteoporosis), include the cDMARDs methotrexate, hydroxychloroquine, azathioprine, mycophenolate, leflunomide, or cyclophosphamide depending on the organ affected and how severe the disease is.

About infliximab

Infliximab belongs to a group of medicines called ‘biological drugs’. It is a type of drug which works by reducing the effect of a chemical called tumour necrosis factor-alpha (TNF-α). TNF- α is released in response to a disease or infection as part of the body’s immune response. Infliximab is used to treat several medical conditions including Crohn’s disease, ulcerative colitis and certain types of arthritis such as rheumatoid arthritis and ankylosing spondylitis. Infliximab is used as both to prevent the disease from getting worse, and to reduce the dose of steroids individuals with severe, refractory sarcoidosis are taking.

The policy is for infliximab to be given intravenously as an outpatient day-case once every eight weeks after the patient has completed an initial loading regimen. The treatment is given until the patient stops responding.

The National Institute for Health and Care Excellence (NICE) has published two evidence summaries (not guidance) on infliximab treatment for pulmonary sarcoidosis (NICE, 2016) and for refractory extra-pulmonary sarcoidosis (NICE, 2017).

Neurosarcoidosis is excluded because there is already a decision for routine commissioning of infliximab in refractory or progressive neurosarcoidosis (NHS England, July 2020).

In 2018, NHS England published a not for routine commissioning position for the use of infliximab in progressive pulmonary sarcoidosis due to insufficient evidence (NHS England, November 2018).

Epidemiology and needs assessment

The annual incidence of sarcoidosis in the UK is reported as seven cases per 100,000 with no difference noted between males and females. Around three quarters of patients diagnosed with sarcoidosis are aged between 30 and 60 years. Data from the British Lung Foundation shows that there is a higher prevalence of sarcoidosis in people from Ireland and of Afro-Caribbean descent due to genetic predisposition. Sarcoidosis in children is extremely rare and diagnosis is difficult to determine as sarcoidosis like symptoms may occur due to different diseases in children. (British Lung Foundation, 2022)

The presentation of sarcoidosis varies from mild, acute self-limiting disease to chronic disease involving several organs and causing severe symptoms and functional impairment.

Less severe disease also has high rates of spontaneous remission - it is estimated that 40% of all patients remit within six months (Gibson et al 1996). In contrast, patients with chronic disease suffer from unremitting disease activity, risk of organ failure and symptoms which can severely reduce their quality of life (van Rijswijk et al 2013). This accounts for about 25% of all patients with sarcoidosis (Jamilloux et al 2017).

Anecdotal estimation from the specialist units in England suggest that there is an existing cohort of 200 patients affected by refractory sarcoidosis (excluding neurosarcoidosis). These patients are likely to already be on Trust funded infliximab or alternative off-label treatments. For patients with refractory sarcoidosis there are currently no alternative treatment options, leading to increased morbidity and mortality risk, except in cases of refractory or progressive neurosarcoidosis where NHS England has approved the use of infliximab (NHS England 2020).

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 (Baughman and Lower, 2020). In 2012, 170 patients died from sarcoidosis in the UK (British Lung Foundation, 2022)

Implementation

Inclusion criteria

Adults who:

- have a diagnosis of sarcoidosis based on clinical, laboratory and/or pathological findings **AND**
- have failed to respond to corticosteroids and/or at least one cDMARD **OR**
- are unable to be treated with corticosteroids and/or cDMARD agents due to intolerance or toxicity or contraindication.

Exclusion criteria

Patients who meet the following criteria are not eligible for treatment with infliximab under this policy:

- Individuals with contraindications to infliximab, as outlined in the summary of product characteristics (SmPC), particularly individuals with any of the following:
  - hypersensitivity to the active substance
  - active and untreated tuberculosis (TB) or other severe infections such as sepsis, abscesses, and opportunistic infections
  - moderate or severe heart failure (NYHA class III/IV) not due to cardiac sarcoidosis[1].
- Individuals with neurosarcoidosis[2]

Starting criteria

A diagnosis of refractory sarcoidosis and initiation of infliximab should be agreed with a suitable multi-disciplinary team (MDT) which includes at least two consultants with experience in the treatment of refractory sarcoidosis and use of infliximab.

A chest x-ray and interferon gamma release assay to investigate for latent TB should have been carried out within the six months prior to commencement of infliximab.

In line with best practice, a hepatitis B and C, and human immunodeficiency virus (HIV) screen should also be carried out within the six months prior to commencement of infliximab.

Stopping criteria

A decision to stop using infliximab should be made by the treating clinician if one of the following occur:

- a serious adverse event e.g., anaphylaxis or severe allergic reaction related to the infusion **OR**

[1] If infliximab is used to treat cardiac sarcoidosis, careful assessment weighing the benefits versus the risks needs to be made to treat a patient, and treatment needs to be managed in a specialist cardiac centre.
[2] There is already a decision for routine commissioning of infliximab in refractory or progressive neurosarcoidosis (NHS England, July 2020).

- no evidence of clinical response within six months of starting treatment identified using the relevant assessment(s) such as:
    - clinical parameters such as lung function tests and/or thoracic imaging (chest x-ray, CT, CT PET)
    - cardiac imaging such as echocardiogram (ECHO) or cardiac MRI
    - laboratory tests such as renal function, liver function, calcium etc
    - disease activity score such as DAS, swollen tender joint count, CSAMI, etc.
    - physician and patient assessment scores such as visual analogue scale or King's Sarcoidosis Questionnaire.

Dose

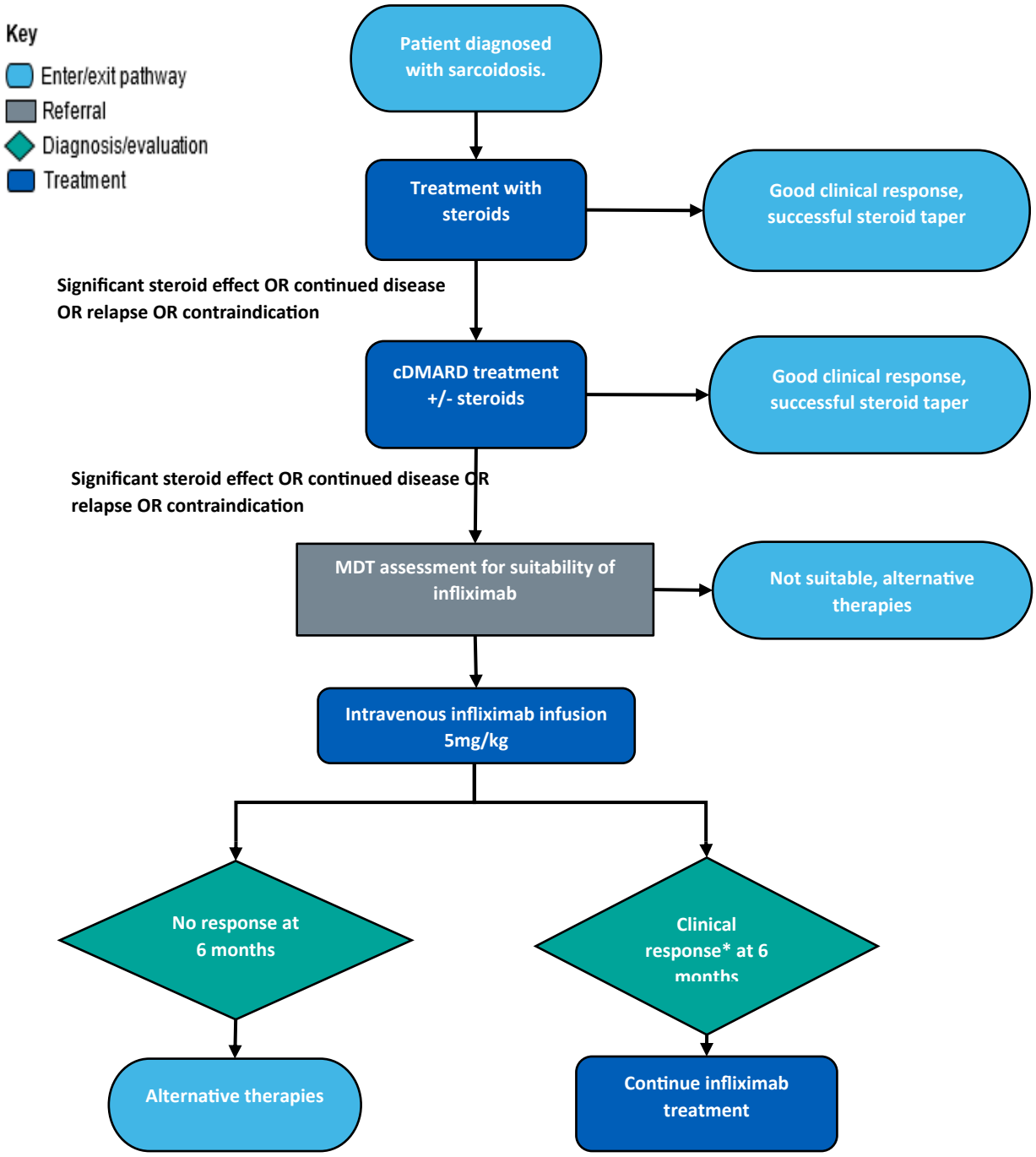
Infliximab is given intravenously. Initial dose of 5 mg/kg, then 5 mg/kg at week two and week six, then 5 mg/kg every eight weeks. This is normally given as an outpatient day case.

If a patient develops secondary non-drug response, intervals between infusions may be reduced, e.g., to every six weeks.

Monitoring

The monitoring requirements for infliximab are in the SmPC and should be followed accordingly.

Patient pathway



*Clinical response identified using the relevant clinical, pathological, and radiological assessment(s) listed above.

Governance arrangements

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as

outlined. Patients continuing treatment beyond six months will also require registering with continuation prior approval software.

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Please note that this is an off-label use of infliximab, therefore Trust policy regarding unlicensed medicines should apply.

Mechanism for funding

Infliximab for the treatment of refractory sarcoidosis (excluding neurosarcoidosis) will be commissioned and funded by NHS England under existing arrangements for the provision of specialised services.

Audit requirements

Data will be reviewed through use of prior approval forms. A national registry will be established to collate data on clinical outcomes from infliximab treatment, with support from the British Thoracic Society, which already has an established pulmonary sarcoidosis registry. It is essential that the national registry collects clinical treatment and clinical outcome data on patients treated via this policy in a timely, regular, and accurate manner. Such data should, at minimum, include demographic patient information, reasons for treatment (i.e., which eligibility criteria apply), measurements of criteria where such apply, as well as the clinical outcome(s) of treatment at 6 months [whether symptoms and/or criteria have been alleviated. This includes the use of relevant tools and assessments, such as results of DAS, CSMI or KSQ. All clinicians prescribing infliximab for refractory sarcoidosis (excluding neurosarcoidosis) must ensure that any additional data collection requirements are met for the purpose of relevant audit and evaluation. The information is collected to inform future policy revisions.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations

between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Checklist Individual Strength (CIS)-Fatigue score	Checklist Individual Strength; fatigue severity dimension: higher scores indicate greater fatigue, cut-off score of 35 for severe fatigue.
Corticosteroids	Corticosteroids are synthetically produced steroids that are mainly used to reduce inflammation and suppress the immune system.
Cutaneous sarcoidosis activity and morphology instrument (CSAMI)	A score developed to capture disease activity and morphological type of cutaneous sarcoidosis.
Disease Activity Score (DAS)	The Disease Activity Score (DAS) and the DAS28 have been developed to measure disease activity in rheumatoid arthritis (RA) both in daily clinical practice as well as in clinical trials, on a group as well as individual level. The DAS/DAS28 is a continuous measure of RA disease activity that combines information from swollen joints, tender joints, acute phase response and general health.
Echocardiogram (ECHO)	An imaging test that uses ultrasound to monitor the heart function.
Human immunodeficiency virus (HIV)	A virus that attacks the body's immune system. There is currently no effective cure for HIV, and once someone acquires HIV, they live with HIV for life. However, there is now effective medication which reduces the viral load and stops the transmission of HIV to others.
Intravenous	This is a form of medicine administration whereby the medicine is given via a needle into a vein in the arm.
King's Sarcoidosis Questionnaire (KSQ)	An online health measure that can quickly assesses how sarcoidosis is affecting a patient's health. It is a subjective view of the patient on how their disease is affecting them.
Multidisciplinary Team (MDT)	MDTs consist of practitioners and professionals from health, care and allied disciplines and sectors that work together to provide holistic, person-centred and coordinated care and support.

The National Institute for Health and Care Excellence (NICE)	NICE provides national guidance and advice to improve health and social care. NICE is an executive non-departmental public body, sponsored by the Department of Health and Social Care.
Neurosarcoidosis	Neurosarcoidosis is a manifestation of sarcoidosis in the nervous system.
Patient's Global Assessment (PGA) scale	Patient Global Assessment score: visual analogue scale 0-100, higher scores indicate lower quality of life.
Refractory sarcoidosis	Refractory disease is defined as sarcoid disease that has failed to respond to corticosteroids and/or at least one Disease Modifying Anti-Rheumatic Drug (DMARD) or where there is contra-indication or intolerance in treatment with those agents (current standard care).
Secondary non-drug response	This refers to when a patient who was previously responding well to infliximab subsequently starts to show a reduced response on repeat dosing and therefore may need shorter intervals between doses to obtain the same response achieved at receiving infliximab every 8 weeks.
Short Form-36 (SF-36)	Physical functioning subscale or total score (physical and mental health subscales combined). 0-100 scale: lower scores indicate lower quality of life.

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