Clinical Commissioning Policy: Infliximab for Progressive Pulmonary Sarcoidosis in adults

NHS England Reference: 170088P

Clinical Commissioning Policy: Infliximab for Refractory Pulmonary Sarcoidosis

First published: November 2018

Prepared by NHS England Specialised Services Clinical Reference Group for Specialised Respiratory

Published by NHS England, in electronic format only.

Gateway reference: 07603

Contents

Policy Statement

NHS England will not routinely commission infliximab for progressive pulmonary sarcoidosis in adults in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

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.

Plain Language Summary

About Progressive Pulmonary Sarcoidosis

Sarcoidosis is a condition where cells in the body clump together to make small lumps called granulomas. When the lungs are affected, it is called pulmonary

sarcoidosis. Progressive pulmonary sarcoidosis occurs when the condition does not respond to the usual treatments.

About current treatments

Most patients with sarcoidosis do not require treatment and often make a full recovery. However, around a third of patients have more serious disease involving different organs and require therapies such as steroids and drugs that suppress the immune system.

About the new treatment

Infliximab is a type of drug which works by neutralising the effect of a chemical called tumour necrosis factor – alpha which is released during an immune response.

What we have decided

NHS England has carefully reviewed the evidence to treat progressive pulmonary sarcoidosis with infliximab. We have concluded that there is not enough evidence to make the treatment available at this time.

1 Introduction

Sarcoidosis is a systemic granulomatous disease of unknown aetiology characterised by multi-organ involvement. Almost 90% of patients have pulmonary involvement but many of these will also show involvement of other organs, typically, skin and eyes (uveitis). Less commonly the central nervous system and heart are involved and these are often organ- and life- threatening. Most patients have a benign disease course but the exact number of patients who spontaneously remit is unknown. When the lungs are affected there may be wheezing, shortness of breath or chest pain. The long-term effects of treatment on the natural history of disease are also unclear. End-stage respiratory disease occurs in a small number of patients. Overall mortality in sarcoidosis is 1% -5% usually due to pulmonary, cardiac or neurological involvement and their complications.

Oral corticosteroids are the first line therapy for patients with progressive disease or end-organ dysfunction, with a maintenance dose for a period of 6-24 months. Other immunosuppressive or anti-inflammatory treatments are considered when corticosteroids fail to control disease progression, or when corticosteroids are contraindicated (typically when patients also have diabetes mellitus and osteoporosis), and if side effects are intolerable. Azathioprine and Methotrexate are the second line drugs of choice. Severe fibrotic pulmonary sarcoidosis may necessitate lung transplantation.

Infliximab has been used by some clinicians in the treatment of progressive pulmonary that does not respond to first or second line treatment. Infliximab is a monoclonal antibody that binds to tumour necrosis factor alpha (TNF-α) and inhibits its functional activity. It is currently licensed as a treatment for other immune-mediated diseases such as rheumatoid arthritis and Crohn's disease. However, Infliximab does not have a license or marketing authorisation for sarcoidosis.

A review of the current literature for Infliximab in the treatment of progressive pulmonary sarcoidosis has been carried out and informs the development of this clinical commissioning policy.

2 Definitions

Sarcoidosis - a systemic granulomatous disease of unknown aetiology characterised by multi-organ involvement.

Progressive pulmonary sarcoidosis - sarcoidosis affecting the lungs which is progressively worsening, despite first and second line treatments.

Sub-optimally treated progressive pulmonary sarcoidosis - sarcoidosis which is progressive in part because usual treatment cannot be used as the side effects are intolerable, organ- threatening or contra-indicated.

Extra-pulmonary sarcoidosis - sarcoidosis affecting organs other than the lungs. Having extra-pulmonary sarcoidosis does not preclude co-presence of pulmonary sarcoidosis.

Infliximab - a chimeric monoclonal antibody against tumour necrosis factor alpha (TNF-α).

3 Aims and Objectives

The policy considered: the clinical circumstances in which NHS England might commission and fund the use of Infliximab in the treatment of progressive pulmonary sarcoidosis.

The objectives were to:

- assess the evidence for the clinical effectiveness, safety and cost effectiveness of Infliximab in the treatment of progressive pulmonary sarcoidosis.
- clarify the commissioning position of NHS England and ensure equitable use of Infliximab as a treatment for patients with progressive pulmonary sarcoidosis.

4 Epidemiology and Needs Assessment

Sarcoidosis is characterised by non-caseating granulomas (non-necrotising nodules of inflammation and scarring) in affected organs. The cause of sarcoidosis is not known.

General Practice data suggests an incidence of approximately three per 100,000 person years for sarcoidosis in the UK. Incidence is highest in people aged 20 to 50 years and appears to be higher in Afro-Caribbean people and marginally higher in women (NHS England 2017). Sarcoidosis in children is extremely rare and diagnosis is difficult to determine as sarcoidosis like symptoms may occur due to different disease aetiology in children.

The presentation of sarcoidosis varies considerably from mild, acute self-limiting disease to chronic disease involving several organs and causing severe symptoms and functional impairment. The condition is staged from I (least severe) to III (most severe): 55% to 90% in patients presenting with stage I disease, 40% to 70% in patients with stage II disease and 10 to 20% of patients with stage III disease.

It often runs a benign course with 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).

The most commonly affected organ is the lung, which is affected in more than 90% of people with sarcoidosis. The second most commonly affected organ is the skin, and other organs such as the eyes, brain, nervous system, liver and heart can also be affected. Estimates for cases with neurological involvement vary from 5% to 15%. It should be noted that this group in particular have a poor prognosis and present with severe acute events, e.g. optic neuritis and blindness, acute hydrocephalus and coma or progressive lower limb weakness (NHS England 2017).

Disease-related mortality is about 5%, with the most common causes of death being lung, cardiac and neurological disease that is refractory to therapy (NICE 2017).

5 Evidence Base

NHS England has concluded that there is not sufficient evidence to support the routine commissioning of this treatment for the indication.

The evidence identified for the use of infliximab for refractory or progressive pulmonary sarcoidosis and/or neurosarcoidosis included one phase II randomised controlled study, one uncontrolled prospective study and six uncontrolled retrospective studies. The one phase II randomised double blind controlled trial compared infliximab to placebo. Improvements were reported in both groups of patients in this study. However no significant differences between the groups were reported. This trial closed early due to poor recruitment and was therefore underpowered to detect a difference between the groups. The results of this study should be treated with caution.

The uncontrolled studies generally reported improvements from baseline with infliximab on a range of outcome measures. In the five studies reporting clinical response, the majority of patients were judged to have shown an improvement by a clinician and in one study 73% of patients reported an improvement in their symptoms. When measures of quality of life, inflammatory response and severity of organs affected were reported a statistically significant improvement was seen. Improvements in pulmonary function and reductions in corticosteroid use were also reported in multiple studies but these did not always reach statistical significance. The clinical meaningfulness of the improvements reported was not always clear.

The proportion of patients experiencing adverse events with infliximab was generally fairly high, as was the proportion of patients experiencing infections and discontinuing infliximab.

The populations in the uncontrolled studies were not always restricted to patients with only pulmonary and/or neurosarcoidosis. However they reported outcomes, such as pulmonary function parameters, separately for patients with a pulmonary treatment indication or reported outcomes for individual organs.

The only comparative study identified for the population of interest was published in 2006 and more recently published evidence for patients with refractory or progressive pulmonary and/or neurosarcoidosis is from uncontrolled studies only. It

is not clear whether evidence from higher quality studies is likely to be published in the future.

In conclusion, Infliximab was generally associated with improvements from baseline in uncontrolled studies on a range of outcome measures with these improvements often reaching statistical significance. However, the evidence base was limited to a small, underpowered phase II RCT and uncontrolled studies, most of which were retrospective studies which are at risk of selection bias. The limitations of the evidence base limit the strength of any conclusions that can be drawn.

6 Documents Which Have Informed this Policy

NICE (2016): Pulmonary sarcoidosis: infliximab. Evidence summary 2 nice.org.uk/guidance/es2

NICE (2016): Refractory extrapulmonary sarcoidosis: infliximab. Evidence summary 4 nice.org.uk/guidance/es4

7 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

References

Atkins C. Wilson AM. (2017) Managing fatigue in sarcoidosis – a systematic review of the evidence. *Chron. Respir. Dis.* 14(2): 161-173.

Baughman RP. Drent M. Kavuru M. Judson MA. Costabel U. du Bois R. Albera C. Brutsche M. Davis G. Donohue JF. Muller-Quernheim J. Schlenker-Herceg R. Flavin S. Lo KH. Oemar B. Barnathan ES on behalf of the Sarcoidosis Investigators. (2006). Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Resp Crti Care Med* 174: 795-802.

British Lung Foundation (2016): The Battle for Breath.

Cohen Aubert F. Bouvry D. Galanaud D. Dehais C. Mathey G. Psimaras D. Haroche J. Pottier C. Hie M. Mathian A. Devilliers H. Nunes H. Valeyre D. Amoura Z. 2017. Long-term outcomes of refractory neurosarcoidosis treated with infliximab. *Journal of Neurology* 264: 891-897.

Chapelon-Abric C. Saadoun D. Biard L. Sene D. Resche-Rigon M. Hervier B. Costedoat-Chalumeau N. Drier A. Leger JM. Cacoub P. 2015. Long-term outcome of infliximab in severe chronic and refractory systemic sarcoidosis: a report of 16 cases. *Clinical and Experimental Rheumatology* 33: 509-515.

Drent M. Cremers JP. Jansen TL. Baughman RP. 2014. Practical eminence and experience-based recommendations for use of TNF-α inhibitors in sarcoidosis. *Sarcoidosis Vasculitis and Diffuse Lung Diseases* 31: 91-107.

Gibson GJ. Prescott RJ. Muers MF. Middleton WG. Mitchell DN. Connolly CK. Harrison BD. (1996) British Thoracic Society Sarcoidosis study: effects of long term corticosteroid treatment. *Thorax.* 51(3): 238-47.

Hostettler KE. Studler U. Tamm M. Brutsche MH. (2012). Long-term treatment with infliximab in patients with sarcoidosis. *Respiration* 83: 218-224.

Jamilloux Y. Cohen-Aubert F. Chapelon-Abric C. Maucort-Boulch D. Marquet A. Pérard L. Bouillet L. Deroux A. Abad S. Bielefeld P. Bouvry D. André M. Noel N. Bienvenu B. Proux A. Vukusic S. Bodaghi B. Sarrot-Reynauld F. Iwaz J. Amoura Z. Broussolle C. Cacoub P. Saadoun D. Valeyre D. Sève P. the Groupe Sarcoïdose Francophone. 2017. Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: a multicenter study of 132 patients. *Seminars in Arthritis and Rheumatism* Mar 8 Epub ahead of print.

Maneiro JR. Salgado E. Gomez-Reino JJ. Carmona L. (2012) Efficacy and safety of TNF antagonists in sarcoidosis. Data from the Spanish Registary of Biologics BIOBADASER and a systematic review. *Seminars in Arthritis and Rheumatism* 42(1): 89-103.

National Institute for Health and Care Excellence. 2017. Refractory extrapulmonary sarcoidosis: infliximab. January 2017.

National Institute for Health and Care Excellence. 2016. Pulmonary sarcoidosis: infliximab. December 2016.

Ørum M, Hilberg O, Krag S *et al.* (2012): Beneficial effect of infliximab on refractory sarcoidosis. *Danish Medical Journal* 59: A4535

Rossman MD. Newman LS. Baughman RP. Teirstein A. Weinberger SE. Miller Jr W. Sands BE. 2006. A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. *Sarcoidosis Vasculitis and Diffuse Lung Diseases* 23:201-208.

Russell E. Luk F. Manocha S. Ho T. O'Connor C. Hussain H. 2013. Long term follow-up of infliximab efficacy in pulmonary and extra-pulmonary sarcoidosis refractory to conventional therapy. *Seminars in Arthritis and Rheumatism* 43: 119-124.

The British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society (2008): Interstitial lung disease guideline. *Thorax* 63: v1–v58

van Rijswijk HNAJ. Vorselaars ADM. Ruven HJT. Keijsers RGM. Zanen P. Korenromp IHE. Grutters JC. 2013. Changes in disease activity, lung function and quality of life in patients with refractory sarcoidosis after anti-TNF treatment. *Expert Opinion on Orphan Drugs* 1(6): 437-443.

Vorselaars ADM. Crommelin HA. Deneer VHM. Meek B. Claessen AME. Keijsers RGM. Van Moorsel CHM. Grutters JC. 2015. Effectiveness of infliximab in refractory FDG PET-positive sarcoidosis. *Eur Respir J* 46: 175-185.

Witek TJ. Mahler DA. (2003) Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *European Respiratory Journal* 21: 267-272.