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

Infliximab for the treatment of refractory pulmonary sarcoidosis that has not responded to corticosteroids and other immunosuppressants (OW23)

February 2023

ONE WALES INTERIM DECISION

Infliximab for the treatment of refractory pulmonary sarcoidosis that has not responded to corticosteroids and other immunosuppressants

Date of advice: February 2023

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been endorsed by health board Chief Executives.

Using the agreed starting and stopping criteria, infliximab can be made available within NHS Wales for the treatment of refractory pulmonary sarcoidosis that has not responded to corticosteroids and other immunosupressants.

Infliximab should be prescribed on the basis of lowest acquisition cost.

The risks and benefits of the off-label use of infliximab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

One Wales advice promotes consistency of access across NHS Wales.

Starting and stopping criteria for infliximab for the treatment of refractory pulmonary sarcoidosis that has not responded to corticosteroids and other immunosuppressants

Developed in collaboration with the South Wales Interstitial Lung Disease multi-disciplinary team and clinicians in North Wales.

Starting criteria:

If disease modifying drugs are required in pulmonary sarcoidosis corticosteroids in the form of prednisolone is the usual first line of therapy. Second line therapies include hydroxychloroquine, methotrexate, azathioprine, mycophenolate, leflunomide and rarely cyclophosphamide. These are initiated for a variety of reasons including:

- Disease progression or ongoing symptomatic burden despite corticosteroids
- Corticosteroid contraindication (intolerable side effect burden, co-morbidities, patient choice)
- Inability to wean prednisolone below 10mg/ day

If a patient has an intolerable side effect burden or evidence of disease progression despite one of the second line therapies an alternative second line therapy is trialled. Third-line biological agents (infliximab) are only considered in pulmonary sarcoidosis when there is failure of, a contraindication to, or intolerance of, second line therapies. This decision would be made at either the South Wales or North Wales Interstitial Lung Disease multi-disciplinary team meetings.

Screening
Prior to commencing infliximab, pre-screening should be undertaken to exclude:

- Active or latent tuberculosis
- Hepatitis virus or HIV
- Current acute infections (viral, bacterial, fungal or parasitic)
- Moderate to severe heart failure (NYHA class III/IV)
- Pregnancy

Prescribers should consult the relevant Summary of Product Characteristics (SmPC) for other cautions to treatment.

Dose
For pulmonary sarcoidosis the usual starting dose is 3 mg/kg at Weeks 0, 2, 6 and then every 8 weeks afterwards. If necessary the dose may be increased on consultant decision to 5 mg/kg if only a minimal improvement has been observed by the fourth dose. Maintenance treatment might continue for 1 year or 2 years.

The administration of infliximab should be in accordance with the SmPC including the use of any premedications and monitoring requirements.

Concomitant administration with an immunosuppressant is recommended, this is usually the immunosuppressant the patient is currently taking, to reduce the risk of

them developing antibodies to infliximab, which are associated with an increased frequency of infusion reactions.

Outcome data, including the dosing regimen should be collected to inform future policy changes.

The infliximab product available at the lowest acquisition cost should be prescribed.

Monitoring

- Blood tests e.g., FBC, U&E, LFTs, CRP as part of the intial screening and prior to infusion
- Infusion-related reactions including anaphylactic shock
- Injection site for signs of phlebitis

Prescribers should consult the relevant SmPC for any other monitoring requirements and potential adverse effects. The patient should be given the information leaflet and special Alert Card, which will be supplied with the infliximab.
Outcome measures should include: improvement in symptoms, improvement or stabilisation of pulmonary function (forced vital capacity and imaging), quality of life and possible reduction in oral corticosteroid dose.

Stopping criteria:

- No response at 6 months*
- Progression of symptoms
- Toxicity to treatment (that cannot or does not respond to temporary treatment interruption)
- Patient request

For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases at or above 5 times the upper limit of normal), treatment should be discontinued.
*The patient's response to therapy is assessed after 6 months and if the patient has not responded to treatment, infliximab will be discontinued.

References:

Merck Sharp Dohme. Infliximab (Remicade) 100 mg powder for concentrate for solution for infusion. Available at: https://www.medicines.org.uk/emc/product/3831/smpc. Accessed 19 January 2023

Royal Brompton & Harefield NHS Foundation Trust. Guidelines for the use of infliximab in adult patients with sarcoidosis. Oct 2018.

Thillai M, Atkins CP, Crawshaw A et al. BTS Clinical Statement on pulmonary sarcoidosis. Thorax. 2021;76:4-20.

One Wales Medicine Assessment Group summary of decision rationale

Medicine: **infliximab**
Indication**: for the treatment of pulmonary sarcoidosis that has not responded to corticosteroids and other immunosuppressants**
Meeting date: **19 December 2022**

Criteria	OWMAG opinion
Clinical effectiveness	OWMAG notes that the main clinical effectiveness evidence is from one systematic review, two randomised placebo-controlled trials and 10 retrospective/observational studies. There is some evidence of benefit based on pulmonary function tests, symptoms and radiographic imaging. However the data are limited. No new safety issues were identified for this patient cohort. Infliximab would be used as an add on therapy to best supportive care. The limited yet positive reports from experts who had used infliximab to treat refractory pulmonary sarcoidosis were noted. OWMAG considers that the evidence provided demonstrates some clinical effectiveness.
Cost-effectiveness	There is no cost-effectiveness evidence available. The impact of this treatment on quality of life is uncertain.
Budget impact	OWMAG considers the clinical estimate of patient numbers reported to be reasonable. The group acknowledges that budget impact estimates are subject to uncertainty due to uncertainty over the proportion of patients who will escalate to the higher dose. There is also a lack of longer-term discontinuation rate data making it difficult to estimate the proportion of people discontinuing treatment throughout the 2-year timeframe. OWMAG consider that the base case provided in the report is a reasonable estimate of the associated cost to NHS Wales.
Other factors	OWMAG acknowledges that the evidence base for treatments to treat this condition is considered weak. This may in part be down to the parameters measured in the studies that do not adequately capture the benefit of this treatment which may be more about stabilising the disease rather than reversing the decline. There is no alternative licensed therapy and patients may be dependent on steroids to control the disease. Some may go on to receive lung transplantation.

	OWMAG acknowledges the significant burden pulmonary sarcoidosis can have on patients' health and health-related quality of life. However this was not captured in the study data.
Final recommendation	OWMAG recommends the use of infliximab for the treatment of pulmonary sarcoidosis that has not responded to corticosteroids and other immunosuppressants. This recommendation is subject to the development of appropriate start/stop criteria.
Summary of rationale	There is some limited clinical evidence to support infliximab as a relatively safe and effective option for the treatment of pulmonary sarcoidosis that has not responded to corticosteroids and other immunosuppressants. Real world data will be captured to assess the benefit of this treatment for this cohort of patients. A recommendation for treatment must be made through the All Wales Interstitial Lung Disease multi-disciplinary team, as appropriate.

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