**NHS ENGLAND SPECIALISED SERVICES**

# CLINICAL PANEL REPORT

Date: January 2023

Intervention: Infliximab

Indication: refractory sarcoidosis (excluding neurosarcoidosis) (adults and children six years and above)

URN: 2204

Gateway: 2, Round 1

Programme: Internal Medicine

CRG: Specialised Rheumatology

---

**Information provided to the Panel**

Policy Proposition

Clinical Priorities Advisory Group Summary Report

Equalities and Health Inequalities (EHIA) Assessment

Patient Impact Assessment (PIA) Report

Evidence Review by Solutions for Public Health

Evidence to Decision Making Summary

Blueteq™ Forms – Initial and continuation

Policy Working Group Appendix

---

This Policy Proposition recommends the routine commissioning of infliximab for refractory sarcoidosis for adults and children aged six years and above. Neurosarcoidosis is excluded from this proposition as there is already an NHS England published policy in place with infliximab as the intervention. Infliximab is a biologic drug which works by reducing the effect of tumour necrosis factor-alpha (TNF-α), thus reducing the build-up of the granulomas in sarcoidosis. This would be an off-label use of the medicine.

Clinical Panel was presented with the evidence review supporting the proposition which included seven studies, including one small randomised controlled trial (n=19), one prospective case series and five retrospective case series with a range of 30 – 56 participants.

The critical outcomes were of low to very low certainty. Mortality – no statistical significance was reported, one death reported whilst receiving infliximab, none within the placebo group. Two case series reported statistically significant improvements from baseline in fatigue severity and physical functioning at 18 weeks to 6 months. Statically significant improvement in steroid use reduction was reported across several case series.

All evidence relating to important outcomes were of low to very low certainty. Partial response in disease activity was seen in 67-96% participants at 6-12 months. Some improvements seen in lung function and radiographic changes.

No evidence was identified for cost effectiveness.

Panel members discussed the proposition and the evidence base at length. They considered that quite a few revisions were required for clarification and strengthening of the proposition.

EHIA – no amendments requested.
PIA – no amendments requested.

---

**Recommendation**

Clinical Panel recommends this return to a future Panel meeting with revisions addressed as outlined.

---

**Why the panel made these recommendations**

Clinical Panel members considered that a decision could not be reached regarding whether this should proceed as routine commissioning as a number of revisions are required.

---

**Documentation amendments required**

**Policy Proposition:**

- Summary –
    - The licence for infliximab is not in relation to sarcoidosis so the sentence referring to why the use excludes children under 6 years old needs to be written more clearly. The licence is in inflammatory bowel disease.
- Definition of refractory is needed as this is not currently clear.
- Inclusion criteria –
    - needs to state the stage of the disease for these eligible patients. It is not clear if the staging referred to the proposition refers to lung disease only. This is a multi-system so the severity for all the relevant conditions needs defining.
- Starting criteria – MDT -
    - reference to subspecialties – what does this means versus speciality. This should be clarified.
    - Reference to ‘significant experience’. Policy Working Group needs to review this use of language and perhaps change to ‘appropriate organ specific experienced clinicians’ to make it clearer.
- Stopping criteria –
    - It is not clear what ‘clinical response at 6 months’ means. It is not currently defined and needs to be as this is key in the treatment pathway. Provide criteria in the proposition for what a clinically meaningful response is.
- Governance arrangements –
    - need to include stronger language regarding data requirements in order to effectively review long term outcomes. Data registry and data linkage needs including.
    - Include the standard policy wording regarding the Trust governance required in the use of off-label medicines.

**Policy Working Group:**

- This is currently a large group and needs reviewing as to having a smaller membership involved in the drafting of the proposition and supporting document, then involving the larger group to review/comment on drafts.

---

Declarations of Interest of Panel Members: None

Panel Chair: James Palmer, Medical Director, Specialised Services

**Response to panel:**

| **Policy proposition** | |
|---|---|
| **Amendment requested** | **Action** |
| **Summary** | |
| The licence for infliximab is not in relation to sarcoidosis so the sentence referring to why the use excludes children under 6 years old needs to be written more clearly. The licence is in inflammatory bowel disease. | Actioned.<br>Wording amended *(Summary, page 2)* |
| Definition of refractory is needed as this is not currently clear. | The definition is in line with all other policies where the term refractory is used. *(Appendix 1)*<br>As no evidence was found for progressive sarcoidosis, the term 'progressive' has not been included in the policy proposition to avoid confusion.<br>Definition wording in policy proposition (*About sarcoidosis, page 3)*:<br>*Refractory sarcoidosis is defined as sarcoid disease that has failed to respond to corticosteroids and/or at least one conventional Disease Modifying Anti-Rheumatic Drug (cDMARD), or where there is contra-indication or intolerance to treatment with those agents.* |
| **Inclusion criteria** | |
| Needs to state the stage of the disease for these eligible patients. It is not clear if the staging referred to the proposition refers to lung disease only. This is a multi-system so the severity for all the relevant conditions needs defining | • Wording related to staging in policy proposition under the subheading 'Epidemiology and needs assessment' has been removed. *(Page 4)* Historically only pulmonary sarcoidosis was staged, but this is used less in clinical practice now. There is no staging for other organ manifestations of sarcoidosis. As this policy proposition is for multisystem sarcoidosis, the PWG did not feel it would be beneficial to include staging that only |

| | |
|---|---|
| | applies to one organ in the inclusion criteria.<br>• The definitions used for refractory and progressive in the evidence review were:<br>*<u>Refractory sarcoidosis</u> 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).*<br>*<u>Progressive disease</u> is defined as aggressive disease that manifests with risk of loss of organ function and/or risk to life and/or significant impairment of quality of life. Studies of patients with any form of chronic sarcoidosis treated with tumour necrosis factor alpha (TNF-α), where there was no indication that their disease was refractory to standard treatment, or that standard treatment is contraindicated were considered for inclusion in this evidence review.*<br>No evidence was identified for progressive disease. The PWG therefore felt it was not appropriate to specify the severity of disease required for treatment with infliximab as this might make it seem that they were trying to include progressive sarcoidosis in the policy, despite there being no evidence. They have therefore avoided making any reference to disease severity in the policy proposition.<br>Additionally, as the refractory definition for the evidence review did not state that patients had to have severe disease, the PWG felt this would be an unnecessary stipulation to put in the policy proposition and may inadvertently end up excluding patients **without** severe disease but **with** refractory disease who would have been included in the population for the evidence review. |
| **Starting criteria – MDT** | |
| Reference to subspecialties – what does this means versus speciality. This should be clarified. | Actioned.<br>Wording amended *(Starting criteria, page 5)* |
| Reference to ‘significant experience’. Policy Working Group needs to review this use of | Actioned. |

| | |
|---|---|
| language and perhaps change to 'appropriate organ specific experienced clinicians' to make it clearer. | Wording amended *(Starting criteria, page 5)* |
| **Stopping criteria** | |
| It is not clear what 'clinical response at 6 months' means. It is not currently defined and needs to be as this is key in the treatment pathway. Provide criteria in the proposition for what a clinically meaningful response is. | Actioned.<br>As sarcoidosis is a multisystem disease, it is difficult to clearly capture a meaningful clinical response for all organ manifestations. There is no standardised assessment of sarcoidosis disease response. The PWG have given examples of how clinical response could be assessed.<br>Wording amended *(Stopping criteria, page 5-6 and Patient pathway, page 7)* |
| **Governance arrangements** | |
| Need to include stronger language regarding data requirements in order to effectively review long term outcomes. Data registry and data linkage needs including. | There is a British Thoracic Society pulmonary sarcoidosis registry but there is lack of funding for this registry. There is no other sarcoidosis registry at present. A new registry needs to be created (or the pulmonary registry expanded) as part of this policy proposition.<br>The specifics of data collection will be covered in the commissioning plan and finance model and should be included in schedule six of the NHS England contract. This is therefore not included in the policy proposition. Funding for the registry needs factoring into the commissioning plan and impact assessment.<br>Wording amended (*Audit requirements, page 8*) |
| Include the standard policy wording regarding the Trust governance required in the use of off-label medicines | Actioned.<br>Wording amended *(Governance arrangements, page 8)* |
| **Policy working group** | |
| This is currently a large group and needs reviewing as to having a smaller membership involved in the drafting of the proposition and supporting document, then involving the larger group to review/comment on drafts. | The revisions were made by the clinical lead and two additional clinicians from the PWG. The changes were then sent round to the whole PWG for comment and consensus. |

**Appendix 1:**

| **Policy title** | **Definition of refractory** |
|---|---|

| | |
|---|---|
| Infliximab for Refractory or Progressive Neurosarcoidosis | Refractory neurosarcoidosis - neurosarcoidosis that has failed to respond to standard treatments (for example corticosteroids and immunosuppressants). |
| Abatacept for refractory idiopathic inflammatory myopathies | Refractory idiopathic inflammatory myopathy is defined as the intolerance to or an inadequate response to glucocorticoids and at least two other conventional immunosuppressive or immunomodulatory agents (1stline treatment), and rituximab second line (which can be given to patients with myositis-specific or myositis-associated antibodies). |
| Rituximab for refractory SLE | For this policy, patients with refractory SLE are defined as those who have used 2 or more disease modifying anti-rheumatic drugs (DMARDs), (one of which must be EITHER mycophenolate or cyclophosphamide, unless contraindicated), and patients still either have:<br>1. ongoing moderate to severe active disease OR<br>2. require excessive use of glucocorticoids (over 7.5mg prednisolone per day) to maintain lower levels of disease activity. |
| Tocilizumab for the treatment of adult-onset Still's disease refractory to second-line therapy (adults) | No improvement in symptoms, and/or inflammatory markers and/or dependence on high dose corticosteroids. |
| Tocilizumab for the treatment of adult-onset Still's disease refractory to second-line therapy (adults) | Only a small proportion of patients with SJIA or AOSD would require treatment with canakinumab after not responding to treatment with NSAIDs, corticosteroids, tocilizumab and anakinra. |
| Canakinumab for patients with Still's disease refractory to anakinra and tocilizumab | Refractory - No improvement in symptoms and/or inflammatory markers and/or dependence on high dose corticosteroids despite treatment. |
| Eculizumab for the treatment of refractory antibody mediated rejection post kidney transplant | The use of the term refractory means that rejection has continued despite the use of the currently recognised treatments. |
| Bortezomib for the treatment of refractory antibody mediated rejection post kidney transplant | The use of the term refractory means that rejection has continued despite the use of the currently recognised treatments. |
| Infliximab (Remicade) as Anti-TNF Alpha Treatment Option for Paediatric Patients with Severe Refractory Uveitis | This policy is for the minority of cases with chronic sight threatening and visually disabling uveitis, refractory to topical and oral steroids and methotrexate. |