Engagement report

Topic details

Title of policy or policy statement:	Canakinumab for patients with Adult Onset Still's Disease (AOSD) refractory to or intolerant of anakinra and tocilizumab (adults and children 2 years and over)
Programme of Care:	Blood and Infection
Clinical Reference Group:	Immunology and Allergy
URN:	2002

1. Summary

This report summarises the feedback NHS England received from engagement during the development of this policy proposition, and how this feedback has been considered.

There have been 7 feedback forms completed and received.

2. Background

Canakinumab is recommended to be available as a routine commissioning treatment option for adults and children 2 years and over with Still's disease refractory to treatment with (or do not tolerate) anakinra and tocilizumab. There is a small population of patients with Still's disease that do not respond to first-, second- or third-line treatment. Canakinumab is proposed as an off-label, fourth-line treatment option. Canakinumab has marketing authorisation, granted by the European Medicines Agency, for use in patients with Still's disease in adults and children aged 2 years and above who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids (EMA, 2019). The proposed use of canakinumab as a fourth-line treatment option is off-label.

Patients should meet all of the following criteria:

- A diagnosis of Still's disease (see patient pathway), including either:
  - Systemic-onset juvenile idiopathic arthritis; OR
  - Adult-onset Still's disease
- Have been treated with DMARDs and not adequately responded[1] or been intolerant as described in NHSE 170056P (adults)[1] or NHSE E03X04 (children)[2].
- Have been treated with anakinra and not adequately responded or been intolerant as described in NICE TA685.

- Have been treated with tocilizumab and not adequately responded or been intolerant as described in NHSE 170056P (adults)[1] or NICE TA238 (children)[2].
- A specialist rheumatology or immunology multidisciplinary team (MDT) agrees that canakinumab is the best option for treatment
    - When treating patients under 18 years this MDT should include a paediatric consultant specialising in rheumatology

Treatment should not be initiated or should be temporarily interrupted in patients with any of the following:

- Hypersensitivity to canakinumab
- Active, severe infection (as per the Summary of Product Characteristics)

This policy proposition has been developed by a Policy Working Group made up of a Clinical Lead, a Lead Commissioner, a Public Health Lead, a Pharmacist, a PPV and 4 additional clinical members.

3. Engagement

NHS England has a duty under Section 13Q of the NHS Act 2006 (as amended) to 'make arrangements' to involve the public in commissioning. Full guidance is available in the Statement of Arrangements and Guidance on Patient and Public Participation in Commissioning. In addition, NHS England has a legal duty to promote equality under the Equality Act (2010) and reduce health inequalities under the Health and Social Care Act (2012).

The policy proposition was sent for stakeholder testing for 2 weeks from 8/9/21 to 22/9/21 The comments have then been shared with the Policy Working Group to enable full consideration of feedback and to support a decision on whether any changes to the proposition might be recommended.

Respondents were asked the following questions:

- Do you support the proposition for canakinumab to be available Still's disease (including systemic juvenile idiopathic arthritis and adult-onset Still's disease) through routine commissioning based on the evidence review and within the criteria set out in this document?
- Do you believe that there is any additional information that we should have considered in the evidence review? If so, please give brief details.
- Do you believe that there are any potential positive and/or negative impacts on patient care as a result of making this treatment option available? If so, please give details.
- Do you have any further comments on the proposition? If Yes, please describe below, in no more than 500 words, any further comments on the proposed changes to the document as part of this initial 'sense check'.
- Please declare any conflict of interests relating to this document or service area.
- Do you support the Equality and Health Inequalities Impact Assessment?

A 13Q assessment has been completed following stakeholder testing. (delete the not applicable paragraphs)

The Programme of Care has decided that the proposition offers a clear and positive impact on patient treatment, by potentially making a new treatment available which

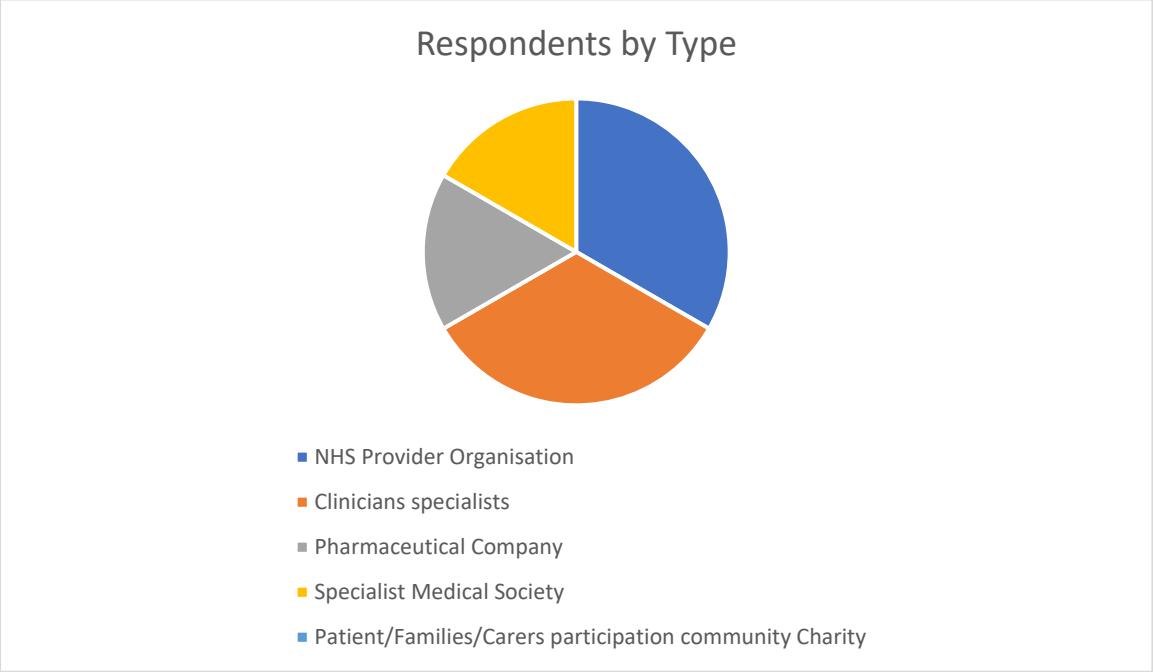
widens the range of treatment options without disrupting current care or limiting patient choice, and therefore further public consultation was not required. This decision has been assured by the Patient Public Voice Advisory Group.

Respondents were asked the following consultation questions:

- RC: Do you support the proposition for Canakinumab for patients with Adult Onset Still's Disease (AOSD) refractory to or intolerant of anakinra and tocilizumab to be available through routine commissioning based on the evidence review and within the criteria set out in this document?
- Do you believe that there is any additional information that we should have considered in the evidence review?
- The impact assessment has been completed to identify the impact of moving from current pathways of care to the one(s) proposed in the draft policy proposition taking into account the anticipated patient numbers, treatment, cost of the treatment and capacity within providers, Do you think that the impact assessment fairly reflects the likely patient numbers, treatment, cost of treatment and the capacity within providers? If not, what do you think is inaccurate?
- The patient pathway describes the patient's journey through the health system to receive current treatment for this condition. Do you think that the policy proposition accurately describes the current patient pathway that patients experience? If not, what is different?
- Please provide any comments that you may have about the potential positive and negative impacts on equality and health inequalities which might arise as a result of the proposed policy that have been described?
- Are there any changes or additions you think need to be made to this document, and why?
- Did you comment on the stakeholder testing for this policy proposition?

4. Engagement Results

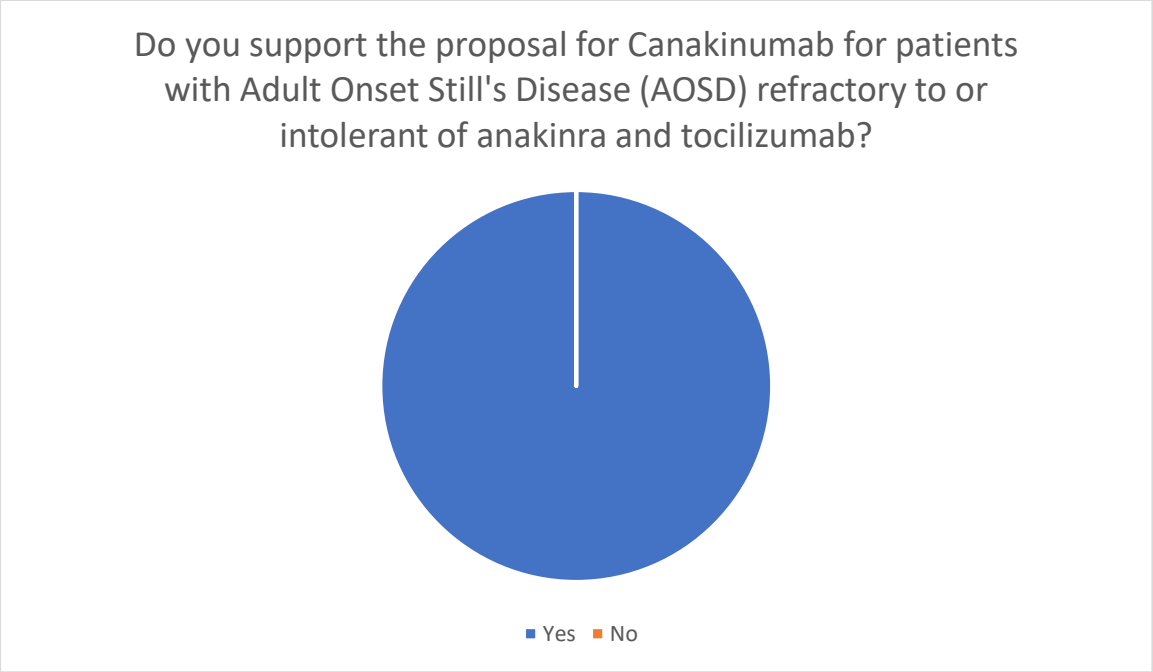
There were 7 responses received: 2 from clinicians representing an NHS organisation treating patients AOSD, 2 clinical specialists, 1 from the pharmaceutical company, 1 from a specialist medical society (British Society of Rheumatology) and 1 from the Rare Autoinflammatory Conditions Community - UK



5. How has feedback been considered?

Responses to engagement have been reviewed by the Policy Working Group and the Blood and Infection PoC. The following themes were raised during engagement:

All responders supported the policy proposition



Keys themes in feedback	NHS England Response
Relevant Evidence	
The position of Methotrexate in the pathway is against the published evidence that has demonstrated that it is ineffective. Therefore, Anakinra and Tocilizumab should be on equal footing to Methotrexate while Canakinumab should be reserved for those resistant to treatment as proposed.	Interesting point but the role of Methotrexate is not in the scope of the current policy proposition
We are delighted that patients with Still's disease should soon have access to Ilaris. We would however like to highlight the fact that Ilaris has been shown to have better patient outcomes if used earlier in the patient pathway. (Please see the references below). Based on CONSIDER – AOSD trial, sJIA trial and RWE, canakinumab consistently demonstrated a rapid and sustained therapeutic effect over the long-term with no unexpected safety issues, and early treatment with canakinumab may reduce chances of chronic disease and permanent damage G. Cavali et. Al. Furthermore, K-Laskari et al 2021, reported that patients refractory to conventional and Biologic therapy with both juvenile and adult onset Stills disease achieved a high level of sustained remission when treated with canakinumab. Similarly, for SJIA patients who discontinued anakinra due to lack of efficacy and tolerability it was observed that canakinumab was also effective and safe de Matteis et al 2021. Based on the Italian consensus on management of AOSD with IL-1s,failure of a first IL-1 inhibitor does not preclude the achievement of a therapeutic response with another IL-1 inhibitor, based on the available efficacy data Colafransceso et al.	The papers are interesting but not relevant to this policy proposition
Impact Assessment	
Positive – Improving patients' quality of life and enabling them to remain independent, access education or employment with less barriers due to their health.	None required
Positive impact for having an additional option that is steroid sparing.	None required
Will vastly benefit patients with i) refractory Still's disease ii) injection/infusion intolerance including allergic reactions to other DMARDs/biologics including anakinra and Tocilizumab.	None required
Treatment is being proposed in a small subgroup of patients with highly resistant disease at risk from steroid related side effects, and infection risk from other ineffective biologic agents and damage from disease activity. Treatment appears likely to improve disease control and hopefully accruing damage and allow reduction of steroid therapy.	None required
We can only foresee a positive impact on patient care as Ilaris has a well-established safety and efficacy profile and offers a convenient dosing schedule for patients. We are delighted that	None required

patients who are suffering from Still's disease, a chronic debilitating disease, should soon be able to have access to Ilaris, the first and only selective IL-1 beta inhibitor licensed for the treatment of Stills. A non-interventional study, which collected real-world patient and caregiver burden and resource use data for biologic-eligible SJIA patients and their families in France, Germany, Netherlands, UK and US (Shenoi S et al., 2016a). ,demonstrated physical impact on the patients' functional ability and the impact of disease on the daily life of the patient, caregiver and their family. These pose a burden on caregivers leading to decreased work productivity, requirement of additional healthcare assistance & increased out-ofpocket expenses. Therefore, by reducing disease activity, canakinumab can improve health-related quality of life and could potentially minimise the impact on healthcare utilisation. Positive • A key cytokine target in SJIA and AOSD. • In the very small proportion of people in whom anakinra/tocilizumab are ineffective, this is a valuable and much needed addition to treatment. Negative • Compared to anakinra that has a short half life the risk of immunosuppression is higher due to longer half life.	
Potential impact on equality and health inequalities	
All 7 responders supported the Equality and Health Inequalities impact assessment.	None required
Changes/addition to policy	
The pathway diagram suggests that in order for sJIA patients to access Anakinra, the patients should have failed Tocilizumab first. This is inaccurate, and the latest commissioning guidelines for Anakinra have made clear that both Tocilizumab and Anakinra can be accessed at the same stage in the pathway as per the physician discretion/choice.	The diagram and the relevant table have been changed on the policy proposition document
Yes Based on Ilaris the Ilaris Summary of Product Characteristics, "Ilaris is indicated for the treatment of active Stills disease including Adult Onset Stills Disease and Systemic Juvenile Idiopathic Arthritis in patients aged 2yrs and older who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids". Therefore, reference to canakinumab use in these patients being off label in the proposed policy is incorrect and use of canakinumab in these populations is entirely consistent with the marketing authorisation for Ilaris. **"Epidemiology & needs assessment" section**	Our Medicines Lead has contacted MHRA who advised it is off-label

We believe that an additional sentence is needed to conclude on the number of AOSD patients who will be eligible for Ilaris. Currently the document only states the number of SJIA patients who will be eligible for Ilaris treatment. Hence, to reflect both AOSD and SJIA patients, we would like to suggest to reflect the number of AOSD patients after this statement; "*It is estimated that less than 20% of patients treated with anakinra or tocilizumab would require treatment with canakinumab. 220 adult patients have been initiated on anakinra or tocilizumab since publication of NHS England 170056P (in July 2018)"*	The second point already included on the policy proposition document.
• Canakinumab Draft Policy Proposition 10-15% of both adults and children with Still's disease present in HLH/MAS (this has a reported mortality of around 11%). They need aggressive initial treatment beyond steroids and cDMARDS and to move to cytokine inhibition within the timeframe that cDMARDS take to be established. Canakinumab is positioned 4th line after tocilizumab (not used in HLH/MAS) and anakinra that is routinely used in HLH/MAS in the context of Still's disease. If patients have evidence of HLH/MAS due to Still's disease that is refractory to anakinra, we would need to move to canakinumab in that circumstance - tocilizumab would be contra-indicated in this scenario as it may paradoxically flare HLH/MAS. In Stills disease, the requirement for the very small proportion who need early aggressive biologic therapy to save their life to 'fail' steroids and cDMARDS makes the practising physicians life difficult and may contribute to morbidity. This comment is supported by the paediatric and adolescent community. In simple terms, there are a proportion of children and adults who are so sick with Stills they can't wait for cDMARDS to work and need rapid escalation to biologic therapy; this principle should be 'built in' to a policy such as this. The term "fourth-line treatment" is ambiguous or not completely helpful. We would suggest using failed, intolerant or contra indication of existing biologic therapy namely Anakinra and Tocilizumab or move to the order of medicines being defined by Stills Disease being refractory to previous therapy. In this case the terminology would become Canakinumab is positioned as treatment for Still disease refractory to steroids, cDMARDS, anakinra and tocilizumab. Complex Stills disease will usually involve MDT discussion. We suggest that the policy recommends that at the point Stills disease is refractory to anakinra and tocilizumab, physicians work as part of an MDT to consider ongoing therapy with key members being Rheumatology and Immunology specialists.	There is separate HLH policy that has been accepted and implemented It is in the title of the policy proposition The MDT is on the algorithm.

For young people under 18 it was noted they would need a paediatric rheumatologist involved in the decision – please amend this to paediatric and adolescent rheumatologist. We are trying to reduce the 'gap' between paediatric and adult rheumatology (and in fact adult rheumatology often 'starts' at age 16) and since adolescence is the period 10-19 many depts have an adolescent rheumatologist who might be excluded unless the terminology is corrected. Is discomfort and inconvenience of daily injection including injection site reactions with Anakinra (in good responders) a reason to switch. Probably is allowing for costs.	In the policy proposition document the term paediatric rheumatologist changed to paediatric and adolescent rheumatologist
• AOSD Evidence Review Canakinumab We need to make people aware that the pathophysiology of SJIA and AOSD are virtually identical. We need to make them aware the AOSD is much rarer than SJIA. We need to point out that Tocilizumab or anakinra are so good in refractory Stills Disease that there is not many patients left who would then move to canakinumab but that these represent a big burden on the health care system. Despite the low evidence from the cited study of 4 patients, we believe that we can extrapolate across indications. So we would take this negative evidence review for AOSD as not being that useful.	
• SJIA Evidence Review Canakinumab The issue with this analysis is that there are few patients who do not respond to cytokine blockers such as anakinra and tocilizumab in SJIA and hence good real world data hard to find In the pivotal NEJM two phase 3 trial papers of canakinumab 80% responded which is impressive, https://www.nejm.org/doi/pdf/10.1056/NEJMoa1205099?articleTools=true So we know that the drug has very good efficacy data.	We are aware of the publication but was not relevant for the evidence review.
To assess real world efficacy of canakinumab (as with other biologic therapies) there could be a he registry to collect data on this to confirm efficacy.	
• Equality and Health Inequalities Impact Assessment Canakinumab for Still's Disease There is a suggestion that children under 2 will be overlooked as drug is not licensed under 2 years. Great care needed as this group may be prone to MAS and possibly have immunodeficiency and canakinumab may not be suitable for some of these cases.	HLH/MAS is the subject of different policy as mentioned above.
• Patient Impact Assessment Canakinumab for Still's Disease	

AOSD can lead to secondary osteoarthritis of large joints and the need for premature joint replacement.	

6. Has anything been changed in the policy proposition as a result of the stakeholder testing and consultation?

The following changes based on the engagement responses have been made to the policy proposition:

- On the current treatment pathway the diagram and the table have been changed to reflect that on SJIA, Tocilizumab or Anakinra can be used as 3rd line treatment option.
- The term *paediatric rheumatologist* changed to *paediatric and adolescent rheumatologist.*

7. Are there any remaining concerns outstanding following the consultation that have not been resolved in the final policy proposition?

None.