

**Clinical
Commissioning Policy
Proposition:
Anakinra/Tocilizumab
for the treatment Adult
Onset Still's Disease
refractory to second-
line therapy(adults)**

Reference: NHS England 1609



First published: **TBC**

**Prepared by NHS England Specialised Services Clinical Reference Group for
Specialised Immunology and Allergy Services**

Published by NHS England, in electronic format only.

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Executive Summary

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 adult-onset Stills Disease

Adult-onset Still's disease (AOSD) is a relatively rare multisystem autoinflammatory disorder of unknown cause. Typically, patients have symptoms of high spiking fever, arthritis in multiple joints, enlarged lymph nodes, rashes, sore throat, an elevated white blood cell count and raised blood markers for inflammation.

There are a number of other recognised clinical symptoms of AOSD including swollen spleen and liver (hepatosplenomegaly), weight loss, muscle pain (myalgia) and swelling around the heart (pericarditis). Diagnosis is difficult due to the wide range of possible diagnoses and lack of specific diagnostic tests.

Stills disease in children is subject to a separate policy as there are significant differences in the course of the illness and its treatment.

About current treatments

Treatment for AOSD consists of the prescribing of anti-inflammatory medicines such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Once the diagnosis is confirmed, patients are initially treated with corticosteroids.

Methotrexate, an immune system suppressant, can be added for patients who fail to achieve remission or are dependent on steroids for symptom control.

Clinical outcomes following treatment of AOSD include decreased severity of the disease or remission, normalisation of white blood cell count and decreased blood markers for inflammation and improvement in quality of life.

About the new treatment

In patients that fail to achieve remission after use of corticosteroids and methotrexate or other disease modifying anti-rheumatic drugs (DMARDs), the use of anakinra and tocilizumab have been suggested as alternative treatments. Anakinra is a medicine that blocks receptors for interleukin-1 (IL-1). IL-1 is part of the complicated process that leads to inflammation. Anakinra is not licensed for use in AOSD.

Tocilizumab has also been suggested as a treatment in AOSD patients with chronic arthritis that does not respond to methotrexate or DMARDs. Tocilizumab is a monoclonal antibody that attaches to the receptor for interleukin-6 (IL-6) which is also part of the process that leads to inflammation. Tocilizumab is not licenced for use in AOSD.

What we have decided

NHS England has carefully reviewed the evidence to treat adult-onset Stills Disease with anakinra and tocilizumab, where the disease does not respond to corticosteroids and DMARDs. We have concluded that there is enough evidence to consider making the treatment available as a third line treatment in these cases.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission the use of Anakinra/Tocilizumab for the treatment of Adult Onset Still's Disease refractory to second-line therapy (adults) and corticosteroids in the treatment of AOSD.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether anakinra and tocilizumab for AOSD will be routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

2 Proposed Intervention and Clinical Indication

AOSD is a relatively rare multisystem autoinflammatory disorder of unknown aetiology with an incidence of approximately 1-2 per million. It is estimated there are between 55-110 incident cases per year and an estimated prevalence of between 400-800 patients in England. Typically patients present with high spiking fever, polyarthritis, lymphadenopathy, evanescent rash, sore throat and a prominent leucocytosis. Acute phase markers such as C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR) and serum ferritin are often raised.

There are a number of other recognised clinical manifestations of AOSD including hepatosplenomegaly, weight loss, myalgia and pericarditis. Diagnosis is difficult due to the wide range of differential diagnoses and lack of specific diagnostic tests.

Various diagnostic criteria have been developed, but the Yamaguchi classification (Yamaguchi 1992) criteria are most frequently used. Five or more criteria are required of which two or more must be major :

Major criteria

- Fever >39 °C, lasting 1 week or longer
- Arthralgia or arthritis, lasting 2 weeks or longer
- Typical rash
- Leucocytosis >10,000/mm³ with >80% polymorphonuclear cells

Minor criteria

- Sore throat
- Recent development of significant lymphadenopathy
- Hepatomegaly or splenomegaly
- Abnormal liver function tests
- Negative tests for antinuclear antibody (IF) and rheumatoid factor (IgM)

Exclusion criteria

- Infections
- Malignancies (mainly malignant lymphoma)
- Other rheumatic disease (mainly systemic vasculitides).

Based on the predominant symptoms, disease activity and evolution, two phenotypes of AOSD have been described. One is a systemic form which has an acute onset. These patients tend to be highly symptomatic with fevers, weight loss and other systemic manifestations (Group 1). In patients with the systemic predominant form, the course of the disease may be self-limiting, intermittent or chronic. The current literature suggests that on average 30% of patients develop a self-limiting course, 30% an intermittent course, and 40% a chronic course.

The other disease type is the arthritis predominant form of AOSD. This usually has an indolent onset (Group 2). Systemic symptoms are less well defined and a subset of patients develop a chronic erosive arthritis.

First line treatment for AOSD consists of NSAIDs and corticosteroids. NSAIDs can be used for symptomatic control during diagnostic work-up. Once the diagnosis is confirmed, patients are initially treated with corticosteroids (0.8-1.0 mg/kg/day).

Methotrexate (MTX) (7.5-20 mg/week) can be added for patients who fail to achieve remission or are dependent on steroids for symptomatic control.

Clinical outcomes following treatment of AOSD include resolution of disease flare, clinical remission, normalisation of biochemical markers, improved serum amyloid levels and improvement in quality of life.

In patients who fail to achieve remission after use of corticosteroids and DMARDs, the use of anakinra has been suggested as a follow on therapy. Anakinra is a biologic agent that blocks receptors for interleukin-1 (IL-1). IL-1 which is important on the pathway that leads to inflammation of joints and joint damage. Anakinra is licensed in combination with methotrexate by the European Medicines Agency (EMA) for use in rheumatoid arthritis (RA) and cryopyrin-associated periodic syndromes (CAPS). Anakinra is not licensed for use in AOSD.

NICE has reviewed anakinra for use in rheumatoid arthritis and does not recommend anakinra for the treatment of rheumatoid arthritis except in the context of a controlled, long-term clinical study (NICE, 2009). The main reasons for this recommendation are that although anakinra in combination with methotrexate was effective, studies suggested that other treatments options appeared more effective and anakinra was not considered cost-effective. NICE has not reviewed anakinra for use in AOSD.

Tocilizumab has also been suggested as a treatment in AOSD patients with the chronic arthritis predominant form (Group 2) refractory to MTX and patients in Group 1 who have failed to respond to MTX and anakinra.

Tocilizumab is a monoclonal antibody that attaches to the receptor for interleukin-6 (IL-6) Which is important on the pathway that leads to inflammation. Tocilizumab in combination with MTX, is licensed for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX and the treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

Tocilizumab is also licensed for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients over 2 years, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.

Tocilizumab can be given as monotherapy or in combination with MTX. NICE has not reviewed tocilizumab for use in AOSD. It has published a technology appraisal guidance (TA238) recommending tocilizumab as a treatment for some children and young people with systemic juvenile idiopathic arthritis that is refractory to standard treatment (NICE, 2011).

NICE has recommended tocilizumab in combination with methotrexate for treating rheumatoid arthritis if the disease activity scores (DAS28) is greater than 5.1 and has not responded to intensive therapy with a combination of conventional DMARDs.

3 Definitions

Adult-onset Still's Disease: a relatively rare multisystem autoinflammatory disorder of unknown cause. Typically patients have symptoms of high spiking fever, arthritis in multiple joints, enlarged lymph nodes, rashes, sore throat, an elevated white blood cell count and raised inflammation markers.

Biologic agent: A substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of diseases. Biologic agents include antibodies, interleukins, and vaccines.

Corticosteroids: group of natural and synthetic analogues of the hormones secreted by the hypothalamic-anterior pituitary-adrenocortical (HPA) axis.

Disease modifying anti-rheumatic drugs: (DMARDs) act by altering the underlying disease rather than treating symptoms. They are not painkillers, but they may reduce pain, swelling and stiffness over a period of weeks or months by slowing down the disease and its effects on the joints.

Inhibitors/blockers: Immunosuppressive agents which inhibit the action of interleukins.

Interleukins: group of cytokines which are synthesized by lymphocytes, monocytes,

macrophages, and certain other cells. They function especially in regulation of the immune system.

Monoclonal antibody: an antibody produced by a single clone of cells or cell line and consisting of identical antibody molecules.

Refractory: no improvement in symptoms, and/or inflammatory markers and/or dependence on high dose corticosteroids

4 Aims and Objectives

This policy proposition considered NHS England's commissioning position for the use of anakinra and tocilizumab refractory to methotrexate and corticosteroids in the treatment of AOSD as a third line treatment.

The objectives were to ensure evidence based commissioning with a view to improving outcomes for patients with AOSD.

5 Epidemiology and Needs Assessment

There is no consensus on the incidence and prevalence of AOSD overall and in Groups 1 and 2 in the English population. Fautrel (2004) states the estimated incidence of AOSD in France is between 1 – 2 cases per million population per year. Therefore, it can be estimated that in England, approximately 55-110 new cases of AOSD could be expected every year, assuming the French and English populations are similar. There is insufficient epidemiological information to make estimates of incidence for each AOSD sub-group.

Fautrel (2004) reports the prevalence of AOSD disease at around 10 per million (range 7.3 to 14.7) in Japan. Asanuma et.al (2015) estimated the prevalence of AOSD disease at 3.9 per 100,000 in a Japanese study. Based on extrapolated estimates for England, approximately 600-800 cases of AOSD could be estimated to be prevalent in the population. Applying this epidemiology should be interpreted with caution given the significant differences in the ethnic and age profiles between the Japanese and English populations. There is insufficient epidemiological information to make estimates of prevalence for each AOSD sub-group.

No evidence was available as regards the proportion of patients thought to be

refractory to methotrexate and corticosteroids with AOSD in the evidence review. Gerfaud-Valentin et al (2014) estimated between a quarter and third of patients with AOSD are thought to be refractory to DMARDs and could require biologicals.

6 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Anakinra

A total of five papers met the inclusion criteria determined on the basis of the research questions in the Population, Intervention, Comparator and Outcomes (PICO). The papers varied significantly in the baseline characteristics of the patients included, the dosage and frequency of drug administration, the use of concurrent therapy and the previous therapies used by the patients. Patients in these studies were predominantly Group 2 (with systemic signs and symptoms and joint manifestations). The published studies have considered a relatively small cohort of patients and no systematic reviews were identified during the literature search. The majority of the studies reviewed were retrospective case series (Ortiz-Sanjuan 2015; Giampetro 2013; Lequerre 2008 and Laskari 2011) and these may be subject to bias in publication, reporting and selection and may not take account of all confounding factors. This may limit the generalisability of the study findings to a larger population.

One open label randomised multicentre study has been included that compares anakinra and DMARDs.

The main outcome measures reported were resolution of disease flares, reduction in steroid dose (steroid sparing) and clinical remission, defined as absence/reduction of fever, joint manifestations and lymphadenopathy along with normalisation or improvement in biochemical markers (Ortiz-Sanjuan 2015; Giampetro 2013; Lequerre 2008, Laskari 2011). Two papers reported physician global assessment score and quality of life (Lequerre 2008; Laskari 2011).

Follow up varied from 12 months (Ortiz-Sanjuan 2015) to 27 months (Lequerre 2008). The studies with shorter follow up periods may not have had sufficient time to

record medium to long term efficacy and safety of the drug. The studies evaluated some patients on anakinra as monotherapy and some where anakinra was given in combination with other drugs (for example methotrexate and/or prednisolone). However as results for all patients were pooled it is not possible to ascertain the specific effect of anakinra as monotherapy.

There appeared to be a greater improvement in systemic signs and symptoms after the introduction of anakinra compared to the improvement in joint manifestations (Ortiz-Sanjuan 2015, Nordstrom 2012; Giampetro 2013, Laskari 2011, Lequerre 2008). Detail was not presented on response by AOSD sub-group and the majority of these patients were taking combination therapy.

Three studies (Ortiz-Sanjuan 2015, Lequerre 2008, and Laskari 2011) reported statistically significant reductions in median corticosteroid dosage after anakinra administration. Anakinra was administered in combination with DMARDs. A statistically significant reduction in ESR and CRP was reported by Lequerre (2008) and Laskari (2011) and significant reduction in the mean number of swollen and tender joints was reported by Lequerre et.al (2008).

Adverse events varied in frequency and severity. The most commonly reported side effects were cutaneous reactions. These included rash (Ortiz-Sanjuan et.al (2015) n=8/41, Lequerre et.al (2008), n= 2/15, Laskari et al (2011) n=3/25), localised injection site reactions (ISR) (one severity grade 1 and one severity grade 2 ISR requiring hospitalisation (Nordstrom et.al 2012, n=12), 2 severe ISRs (Giampetro et al (2013),n=28), Laskari et al (2011) n=5/25) which in some cases lead to discontinuation of medication. Some patients discontinued their medication due to the severity of the rash ((n=2, Ortiz-Sanjuan et.al (2015))

Another commonly reported side effect was infection including urinary tract infections (UTIs), herpes zoster, pneumonia and varicella zoster (Ortiz-Sanjuan et.al (2015) (n=3/41, Laskari et al (2011) n=7/25, Rossi-Semerano et. al. (2015)).

Other side effects reported included single cases of other infections (for example bronchitis), hepatitis and hepatotoxicity.

There were no published studies evaluating the cost-effectiveness of anakinra

and/or comparator therapies in the treatment of refractory adult-onset Still's disease.

Tocilizumab

A total of four papers met the inclusion criteria determined on the basis of the research questions in the PICO. A case series published by Cipriani (2014) (n=11), a retrospective multi-centre open label study by Ortiz-Sanjuan (2014) (n=34), a prospective cohort study by Puechal (2011) (n=14) and a retrospective questionnaire based survey study by Elkayam (2014) (n=15). The papers varied significantly in the baseline characteristics of the patients included, the dosage and frequency of drug administration, the use of concurrent therapy and the previous therapies used by the patients. Patients in these studies were predominantly group 2. It was not possible to separate out the results for the two patient groups which make it challenging to make specific recommendations for each sub-group of AOSD. While most studies state that patients had refractory disease their complete treatment history is not stated, so there may be patients included in the results who may not have had refractory disease.

There were no randomised controlled trials or systematic reviews identified in literature. The design of the studies mean they may be subject to selection, publication and reporting bias and may not take account of all confounding factors. This may limit the generalisability of the studies to a larger population.

The main outcome measures included were impact on systemic disease features (Cipriani 2014), reduction in inflammatory markers (Elkayam 2014) and steroid sparing (Ortiz-Sanjuan 2014, Elkayam 2014). The retrospective nature of some of the studies also limits the range of outcomes measured and reported.

Follow up varied from 6 months (Elkayam 2014 and Puechal 2011) to 12 months (Cipriani 2014 and Ortiz-Sanjuan 2014). The variability in the follow up duration means that long term efficacy and safety of tocilizumab cannot be fully evaluated. The studies evaluated some patients on tocilizumab as monotherapy and some for whom tocilizumab was given in combination with other drugs (for example prednisolone). However as results for all patients were pooled it is not possible to ascertain the specific effect of tocilizumab as monotherapy.

There appears to be evidence of effectiveness in the studies in modifying features of

the disease such as reduction in median disease activity score, significant improvement in joint assessment ($P<0.05$) and Visual Analogue Scale (VAS) global assessment ($P<0.005$) reported (Cipriani 2014). Of the 11 patients in this study 8 patients received tocilizumab in combination with MTX and prednisolone and 3 had tocilizumab with prednisolone only. A statistically significant reduction in mean tender joints was reported by Elkayam (2014) ($P<0.05$). Other studies report on the European League Against Rheumatism (EULAR) scores remission (Cipriani 2014, Puechal 2011) and substantial but not significant reduction in joint manifestations (Ortiz-Sanjuan, 2014). Detail was not presented on response by AOSD sub-group. Elkayam (2014) reports significant reduction in mean ESR and CRP values ($P<0.05$). Two studies reporting a statistically significant steroid sparing effect (Ortiz-Sanjuan 2014, and Elkayam 2014).

Adverse events varied in frequency and severity. The most commonly reported side effect was infection, including upper respiratory tract infections (URTIs), herpes zoster, pneumonia and UTI (Ortiz-Sanjuan et.al (2014) ($n=10/34$), Cipriani et al (2014) $n=1/11$). In some cases this lead to patients discontinuing medication.

Another commonly reported side effect was injection site reaction (Cipriani et al (2014) $n=2/11$). Systemic flare was also reported (Cipriani et al (2014) $n=3/11$). Other side effects reported included single cases of hepatotoxicity.

There were no published studies evaluating the cost-effectiveness of tocilizumab and/or comparator therapies in the treatment of refractory adult-onset Still's disease.

Conclusion

The published evidence on the clinical efficacy and safety of both anakinra and tocilizumab in AOSD consists of case series, retrospective studies, a randomised open label study and a prospective cohort study. These studies are of variable quality. The major drawback of these studies is that they are subject to selection bias and the effect of confounding factors so it is difficult to understand the true efficacy of the intervention.

The evidence suggests that both anakinra and tocilizumab are associated with a

positive impact on biochemical markers, systemic features and use of steroids in patients with refractory AOSD. However as both drugs were administered as both monotherapy and combination therapy their exact effect cannot be ascertained. As patients received different drugs in combination with anakinra and tocilizumab it is not possible to make clear recommendations on which drugs could be given in combination or at which stage of disease progression. Patients who received the drug were from Group 1 and 2 but pooled results were presented so it is not clear which group would most benefit from the therapy.

Adverse events were reported relatively frequently and ranged from injection site reactions to severe infections. The lack of randomised controlled trials may be due to the rarity of the disease and heterogeneous presentations which means it is difficult to make direct comparisons with standard care.

No studies have evaluated the cost-effectiveness of either drug or compared its cost effectiveness with existing treatments.

7 Proposed Criteria for Commissioning

Anakinra or tocilizumab will be routinely commissioned for the treatment in Adult Onset Still's Disease as a third line treatment where patients are refractory to steroid-sparing effect DMARDs.

Anakinra

Anakinra will only be commissioned for those patients who meet the following criteria:

- Patients who have failed to respond to – or are intolerant of - standard immunosuppressive therapy, including at least two of the following agents: methotrexate, cyclosporine, azathioprine, leflunomide, cyclophosphamide and mycophenolate or where standard therapies are contraindicated; AND
- Patients have been provided with information on potential adverse effects of anakinra

Response Criteria for anakinra:

At least two of the following:

- Reduction of DAS28 by at least 1.2 points
- Reduction of ESR by at least 25%
- Reduction of CRP by at least 25%
- Reduction of corticosteroid dose by at least 25%

Dosing

The standard dose is 100mg/daily, but this can be increased to 200mg/daily in patients with inadequate response and also reduced to 50mg/daily in stable patients (this can be administered as 100mg on alternate days)

Stopping criteria:

- Not achieving the response criteria within 8 weeks.
- In patients where the response criteria are achieved but subsequently response to anakinra declines and loses efficacy, as judged by loss of the response criteria above over 2 consecutive assessments, at least 3 months apart.

Tocilizumab

Tocilizumab will only be commissioned for those patients who meet the following criteria:

- Patients who have failed to respond to - or are intolerant of - standard immunosuppressive therapy, including at least two of the following agents: methotrexate, cyclosporine, azathioprine, leflunomide and mycophenolate or where standard therapies are contraindicated ; AND
- Patients have been provided with information on potential adverse effects.

Response Criteria for Tocilizumab:

At least three of the following:

- Reduction of DAS28 by at least 1.2 points
- Reduction of ESR by at least 25%

- Reduction of CRP by at least 25%
- Reduction of corticosteroid dose by at least 25%

Dosing

Dosage can initially start at between 4mg/kg every 4 weeks to 8mg/kg every two weeks. This can then be titrated and reduced once the patient has started to respond. Stable patients could be considered for sub-cutaneous tocilizumab.

Stopping criteria:

- Not achieving the response criteria within 8 weeks.
- In patients where the response criteria are achieved but subsequently response to tocilizumab declines and loses efficacy, as judged by loss of the response criteria above over 2 consecutive assessments, at least 3 months apart.

Clinical consensus suggests that tocilizumab may be chosen in preference to anakinra for patients where joint inflammation predominates and anakinra in preference to tocilizumab where systemic symptoms predominate. For patients where there is no response to anakinra (as defined above), the clinician may consider switching to the tocilizumab and visa versa. Treatments not to be used concurrently.

8 Proposed Patient Pathway

After an initial AOSD diagnosis using a diagnosis criterion such as Yamaguchi criteria the treatment pathway would be

First line treatments: NSAIDS and corticosteroids: prednisolone 0.8-1 mg/kg/day for 4-6 weeks.

Second line treatments: When diagnosis is confirmed, patients treated using a selection of the following conventional steroid-sparing effect DMARDs prescribed in line with NICE Clinical Knowledge Summary (CKS) for DMARDs :

- MTX: 7.5 -25 Mg/week (oral or s/c) or
- Cyclosporine: up to 5mg/kg/day depending on tolerance/side effects

- mycophenolate 2-3g/day or
- Leflunomide 10-20 mg od, or
- Azathioprine 2-2.25mg/kg (in patients with normal thiopurine methyltransferase (TPMT) levels; 1-1.25mg/kg in patients with heterozygote level TPMT levels.)
- Corticosteroids can be used in combination with any of these regimes.

Patients that are refractory too, or are intolerant of two of the above second line treatments can be considered for third line treatment.

Response Criteria for DMARDS:

At least two of the following:

- Reduction of DAS28 by at least 1.2 points
- Reduction of ESR by at least 25%
- Reduction of CRP by at least 25%
- Reduction of corticosteroid dose by at least 25%

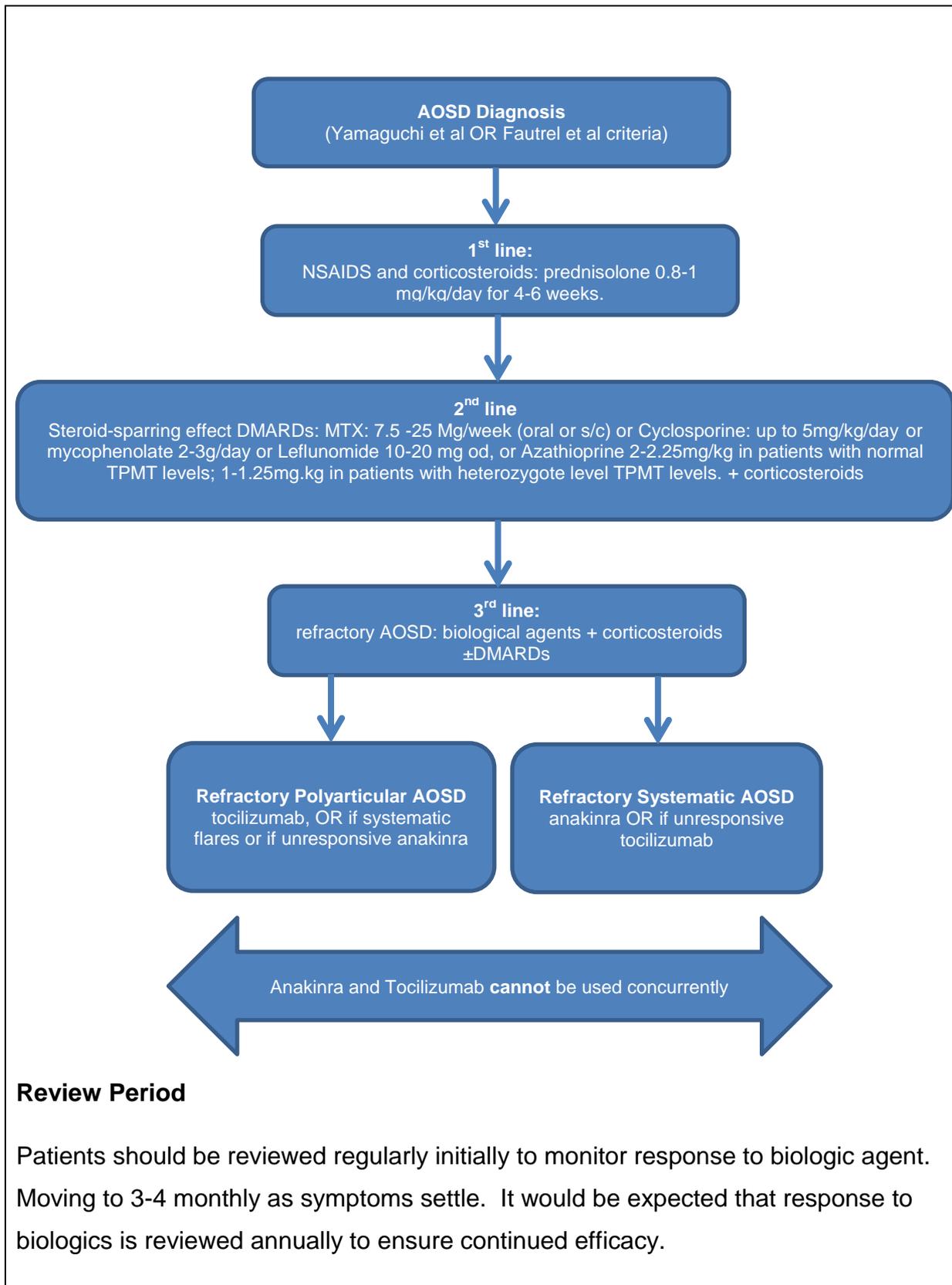
Criteria for third line treatment:

- Not achieving the response criteria within 8 weeks to second line treatments.
- In patients where the response criteria are achieved to second line treatments but subsequently response declines and loses efficacy, as judged by loss of the response criteria above over 2 consecutive assessments, at least 3 months apart.

If the patient is refractory or develops third line treatment can be anakinra or tocilizumab plus corticosteroids ±DMARDs

- Polyarticular AOSD – tocilizumab changing to anakinra if systematic flares or if no response to tocilizumab.
- Refractory AOSD – anakinra changing to tocilizumab if no response to anakinra.

Definitions for response are listed in section 7. Anakinra and tocilizumab are not to be used concurrently.



9 Proposed Governance Arrangements

Anakinra and tocilizumab for AOSD must only be used for treatment in specialised

Rheumatology and/or Immunology centres, or in collaboration with a specialised centre under the supervision of an expert multidisciplinary team.

10 Proposed Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England specialised commissioning team.

11 Proposed Audit Requirements

Treatment centres will use a prior approval system to track and audit use of anakinra and tocilizumab, in order to ensure it is administered according to the criteria for commissioning.

12 Documents That Have Informed This Policy Proposition

The Following document have informed this policy:

- B09/S/a NHS Standard Contract for Specialised Immunology (All Ages)
- A13/S/a NHS Standard Contract for Specialised Rheumatology Services (Adult)
- <https://cks.nice.org.uk/dmards>

13 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

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