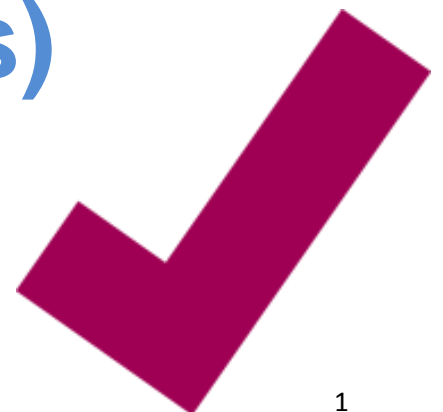


**Clinical  
Commissioning  
Policy Proposition:  
Anakinra to treat  
periodic fevers and  
autoinflammatory  
diseases (all ages)**



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

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Draft for consultation

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# 1 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 periodic fevers and autoinflammatory disease

Periodic fever and autoinflammatory diseases are a group of very rare genetic conditions that occur in children and adults. In this policy, the diseases included are:

- Familial Mediterranean Fever
  - This is the commonest of the inherited fever syndromes and most commonly seen in people of Mediterranean and Middle Eastern origin, affecting adults equally and typically presenting in childhood. The cause of FMF is an abnormality in a gene called MEFV. It is an inherited disease and there are thought to be over 300 different mutations in the gene that cause FMF. The diagnosis, supported by gene testing, relies on the history of recurrent and short attacks of fever and pain.
- Hyperimmunoglobulin D syndrome (HIDS) also known as Mevalonate Kinase Deficiency (MKD)
  - This is an inherited disease, caused by a mutation in the MVF (mevalonate kinase) gene with approximately 60 different mutations having been described. It is commonly seen in people from North Western Europe, is equally common among adults and usually

presents within the first year of life. Symptoms during the attacks include fever, enlarged neck glands, abdominal pain with vomiting and diarrhoea as well as more general symptoms such as aching limbs, large joint arthritis, headache, rash and mouth ulcers.

- Schnitzler's syndrome
  - This is a disease that affects adults of usually 50 years and older and typically presents with a chronic urticarial (nettle-like) rash, fever and fatigue. The cause of Schnitzler's syndrome is not entirely clear, although it has been observed that there is bone marrow involvement in patients with the syndrome.
- Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)
  - This is an inherited disease passed on by both parents associated with mutations in tumour necrosis factor receptor superfamily 1A gene (TNFRSF1A). Many patients have family members affected as only one abnormal copy of the gene is required to cause the disease. TRAPS has been reported in many ethnic groups, adults are equally affected and symptoms usually start before the age of four years. The attacks that patients with TRAPS experience are far less distinct than those seen in FMF; features include fever, limb pains that may slowly move inwards towards the chest or abdomen; abdominal pain, rash, headache, chest pain, enlarged glands and red and swollen eyes. TRAPS attacks are accompanied by blood test abnormalities showing inflammation and genetic testing is necessary in making a diagnosis.

People with all these conditions have an abnormal immune system response that results in recurring bouts of inflammation. The symptoms of inflammation include: high temperature (fever); severe fatigue; severe abdominal, chest or joint pains; headaches; rash; and mouth ulcers. Vital organs may be damaged, including the kidneys and brain.

These diseases can also eventually cause a condition called systemic amyloidosis that affects the kidney and causes kidney failure through build-up of abnormal protein in the tissues.

Prior to definitive diagnosis, some patients have unnecessary investigative surgery, for example, exploratory laparotomy for peritonitis, arthroscopy to exclude infective arthritis, appendectomy, cholecystectomy, surgery for endometriosis. When the symptoms are so severe, they can reduce quality of life and cause significant disability.

### **About current treatments**

The current standard treatments for the conditions covered by this policy aim to 'turn down' the immune response. First line treatments primarily use a range of anti-inflammatory and immune-suppressing drugs including high dose steroids and non-steroidal anti-inflammatory drugs (NSAIDs), for example, ibuprofen; these drugs can help to reduce symptoms in some patients.

These drugs are not always effective and some may cause side effects, particularly the high dose steroids. Repeated courses of some of the drugs, notably steroids, can cause other problems such as weight gain, skin and bone thinning and susceptibility to diabetes and infections.

### **Familial Mediterranean Fever**

- The first line treatment for FMF is a white cell modulating drug called colchicine. The majority of patients with FMF are controlled on colchicine, which has also shown to be effective in preventing amyloidosis. However, in 5-10% of patients, colchicine is not effective and some patients may still develop amyloidosis. Some patients are intolerant of colchicine; the commonest side effect is diarrhoea.

### **Hyperimmunoglobulin D syndrome (HIDS) also known as Mevalonate Kinase Deficiency (MKD)**

- Patients with HIDS or MKD are treated with a variety of medications, including NSAIDs, steroids, and colchicine. These all aim to reduce the effects of inflammation. Response to these treatments is extremely variable, and often poor.

### **Schnitzler's syndrome**

- Therapies such as antihistamines, NSAIDs, steroids, colchicine, hydroxychloroquine and pefloxacin are used as first line treatments for patients with Schnitzler's syndrome. These treatments usually provide only partial or temporary improvement of the symptoms.

### **Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)**

- For patients with TRAPS, the current treatment is usually high-dose steroids and NSAIDs but this does not stop further attacks from occurring. In more severe disease, long-term treatments that may block some of the messengers of inflammation can be very effective in preventing attacks.

### **About the new treatment**

Anakinra is a drug that works to reduce the effect of the chemicals in the body that cause inflammation and an abnormal immune response. This group of chemicals is called the interleukin-1 (IL-1) family. Drugs called interleukin-one blockers have been found to be clinically effective in the treatment of periodic fever and auto-inflammatory diseases that are caused by IL-1. By reducing inflammation, anakinra also reduces the build-up of a protein called serum amyloid A protein (SAA) and therefore reduces its accumulation in vital organs.

The studies in the clinical evidence review support the effectiveness of anakinra. Anakinra is used off label for these conditions; this means that there is no specific licence for this drug to be used in these clinical conditions.

### **What we have decided**

NHS England has carefully reviewed the evidence to treat the following periodic fevers and autoinflammatory diseases with anakinra:

- Familial Mediterranean Fever
- Hyperimmunoglobulin D syndrome (HIDS) also known as Mevalonate Kinase Deficiency (MKD)

- Schnitzler's syndrome
- Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)

We have concluded that anakinra may be used in all the conditions listed above and where the first line treatment is not effective. In the case of Schnitzler's syndrome, we have concluded that anakinra should be used as first line treatment.

## 2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission the intervention.

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 for periodic fevers and autoinflammatory diseases will be routinely commissioned will be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

## 3 Proposed Intervention and Clinical Indication

Periodic fevers and autoinflammatory diseases are a group of very rare disorders characterised by recurrent episodes of systemic and organ-specific inflammation. Abnormal activation of the innate immune system causes intense episodes of fever and inflammation.

These diseases can also cause amyloidosis, a condition in which insoluble proteins are deposited in the organs and tissues. Amyloidosis manifests predominantly as renal failure.

The key clinical features of periodic fever and autoinflammatory disease are: recurrent episodes of systemic inflammation with disabling fever; overwhelming fatigue; and multi-system symptoms including serositis, neutrophilic rash, muco-



cutaneous ulcers, arthralgia/arthritis, myalgia, abdominal pain and aseptic meningitis/headaches. These symptoms can cause significant disability and reduced quality of life.

The specific conditions for which anakinra is under consideration are:

- Familial Mediterranean fever (FMF)
- Hyperimmunoglobulin D Syndrome, (HIDS) also known as Mevalonate Kinase Deficiency (MKD)
- Tumour necrosis factor receptor–associated periodic syndrome (TRAPS),
- Schnitzler syndrome

The current clinical management of periodic fevers and autoinflammatory diseases aims to suppress the inflammatory response with immune-modulating medication and to provide supportive care. This can include use of steroids, non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine (in FMF).

Anakinra works by inhibiting the action of interleukin 1 (IL 1), which has an important role in the pathogenesis of autoinflammatory disease.

Adverse effects associated with anakinra include injection site infections and, rarely, liver toxicity. The risk of adverse effects may be greater in children. However in most cases the side effects are well tolerated.

a) Familial Mediterranean Fever

- The subgroups of patients who are eligible for anakinra are those with FMF who have ongoing symptoms that are resistant to colchicine therapy alone (crFMF) or for patients who are unable to tolerate colchicine due to its side effects

b) Hyperimmunoglobulin D syndrome (HIDS) or Mevalonate Kinase Deficiency (MKD)

- The subgroups of patients who are eligible for anakinra are those in whom standard treatment has failed or in whom standard treatments

are poorly tolerated.

c) Schnitzler's syndrome

- First line use in patients who experience symptoms of a sufficient severity to require treatment.

d) Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)

- The sub group of patients who are eligible for anakinra are those who have a poor response to first line treatments and/or for whom long-term high dose steroid treatment would be the only other option.

## 4 Definitions

### Amyloid A (AA) Amyloidosis

AA amyloidosis occurs in a proportion of patients with chronic inflammatory diseases. Infections and inflammation cause the liver to produce a protein called serum amyloid A protein (SAA) in large quantities. In AA amyloidosis, SAA protein accumulates in vital organs in an abnormal aggregated form and severely damages the kidneys in most cases.

### Anakinra

Anakinra is a recombinant drug that blocks the action of interleukin 1, an important chemical in the inflammatory pathway.

### Colchicine

Colchicine is a drug that modulates white cell function, and is an effective preventative treatment in most patients with FMF and sometimes other periodic fever conditions. Its effectiveness may reduce over time and it may cause intolerable side effects such as diarrhoea

### Quality of Life (QoL)

Quality of Life is a broad measure of a person's health and wellbeing.

## 5 Aims and Objectives

This policy proposition considered: the efficacy and safety of the IL-1 blocking agent anakinra as a treatment for poorly controlled periodic fevers and autoinflammatory diseases including: cr-FMF, TRAPS, HIDS/MKD and Schnitzler's Syndrome.

The objectives were to:

- review the available evidence for the efficacy and safety of anakinra as a treatment for the identified conditions; and
- define the criteria for use.

## 6 Epidemiology and Needs Assessment

These conditions are all very rare. The estimates below are based upon expert clinical advice.

1. Familial Mediterranean Fever  
Incidence <40 new cases a year.  
Prevalence <400 patients in England  
Proportion of patients who may require anakinra: estimated at 20-40 patients, assuming 5-10% of patients will have colchicine-resistant disease, or be unable to tolerate colchicine.
2. Hyperimmunoglobulin D syndrome (HIDS) / Mevalonate Kinase Deficiency (MKD)  
Incidence: <5 new cases a year  
Prevalence <50 patients in England (<300 globally)  
Proportion of patients who may require anakinra: approximately 70%
3. Schnitzler's syndrome  
Incidence: < 5 new cases a year.  
Prevalence <50 patients in England.  
Proportion of patients who may require anakinra: 100% (as anakinra is recommended as the first line treatment for this disease)
4. Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)

Incidence: <10 new cases a year  
Prevalence <100 patients in England  
Proportion of patients who may require anakinra: 75%

The best aggregated estimates for these conditions taken together are:

- Incidence: approx. 40-60 new cases a year
- Prevalence <600, of whom approx. 200 may require anakinra.

## 7 Evidence Base

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

A summary of the evidence review undertaken to inform the policy is provided below:

- Nine papers were identified as eligible from the literature search. Of these papers
  - three present findings on FMF only
  - one on TRAPS only
  - one on HIDS / MKD only
  - one on Schnitzler's only
  - three papers present findings on the treatment and management of a range of periodic fevers and autoinflammatory diseases including: FMF, TRAPS, HIDS/MKD and Schnitzler's syndrome.
- For the purposes of the evidence review, where papers are presenting data on a number of conditions, the evidence and outcomes are reviewed by condition.
- There are very few high quality trials in the use of anakinra. This is due to the rarity of the periodic fevers and autoinflammatory diseases and to the very small numbers of people with clinically defined disease.
- One study is a randomised control trial (RCT), two are cohort studies, two are systematic reviews and the remaining evidence is in the form of retrospective evaluation of cases. This could present a bias as the cases that are actually written up or submitted for review are more likely be the ones for which treatment

was effective.

- Although case studies and retrospective audits are generally considered of lower quality evidence than RCTs, the number of cases showing positive outcomes as a whole is noteworthy, especially when treatment response is usually quick (a matter of days), and shows a significant improvement or resolution in florid disease.
- Because these are rare conditions and cause a range of signs and symptoms, interpretation of treatment outcomes has not been standardised and are subject to a degree of clinician and patient interpretation, although laboratory markers of inflammation are also used in most cases reported here.
- The papers consider treatments for adults and children.
- Treatment safety is included to a greater or lesser degree in the papers, however one paper (Rossi-Semerano et al 2015) provides a detailed breakdown of adverse events in the use of anakinra, but not by condition. The safety of the treatment can also be inferred from the use of anakinra in other conditions such as Cryopyrin-Associated Periodic Syndromes (CAPS) and rheumatoid arthritis.
- The most significant adverse events were injection site reactions, and these should be taken in context with the severity of the overall disease.

The key findings for each indication are as follows:

#### **FMF**

- There were six papers contributing to the assessment of anakinra for cr-FMF (Basaran et al 2015; Ben-Zvi et al 2017; ter Haar et al 2013; van der Hilst et al 2016; Ozen et al 2017; Rossi-Semerano et al 2015).
- The papers included one (RCT of treatment and control which, although a small sample provided the highest grade evidence of all papers reviewed).
- The studies were reviewed for effectiveness (response to treatment) and for safety.
- Response to treatment includes some or all of the following markers: complete, partial or no response using clinical and inflammatory markers; number of attacks; site of attacks; quality of life; and adverse events.
- The patients in all cases were those resistant or intolerant to the first line of treatment colchicine, i.e. cr-FMF.

- The RCT, which can be taken as the strongest evidence, compared two treatment arms of usual treatment and treatment with anakinra and presented a 100% treatment response in the treatment arm (Ben-Zvi et al 2017).
- Using data from all six papers, 109 cases out of 114 showed a complete or partial treatment response (Basaran et al 2015; Ben-Zvi et al 2017; ter Haar et al 2013; van der Hilst et al 2016; Ozen et al 2017; Rossi-Semerano et al 2015).
- The publications all consistently report injection site reactions, due to the vehicle of drug delivery, however, the full extent of adverse events (AEs) were not always reported in detail in the publications reviewed.
- To summarise, anakinra appears to be effective for inadequately controlled FMF, i.e. for patients who do not tolerate or have a poor response to colchicine.

#### **HIDS/MKD**

- The evidence from four papers contributed to this review.
- The papers included,
  - a systematic review of 22 papers on the effect of anakinra (Kostjukovits et al 2015),
  - three retrospective evaluations of a range of periodic fever and autoinflammatory disorders and outcomes from non-IL-1 blockers and with IL-1 blockers (Ozen et al 2017, Ter Haar et al 2013, Rossi-Semerano et al 2015)
- The studies all reviewed the use of biologics (which includes anakinra), except ter Haar et al (2015) which reviewed outcomes from all treatments - biologics and non-biologics.
- All four publications showed a partial response or complete remission (Kostjukovits et al 2015, Ozen et al 2017, Ter Haar et al 2013, Rossi-Semerano et al 2015).
- The papers showed a greater proportion of people achieving a partial response than a complete response, approximately two thirds partial and one third complete, whereas for cr-FMF and TRAPS a complete response is seen in the greater proportion of patients. However the overall rate of any benefit was still high.
- To summarise, anakinra appears to be effective to some degree for inadequately

controlled HIDs, however the proportion of patients achieving complete control is lower than for the other conditions.

### **Schnitzler's syndrome**

- The evidence from two retrospective analyses contributed to this assessment of results.
- The papers included:
  - One retrospective analysis of a range of periodic fever and inflammatory disorders of which Schnitzler's syndrome was one, (Rossi Semerano et al 2015), and
  - one which focused on Schnitzler's syndrome only: Neel et al (2014) compared treatment between patients receiving IL-1 blockers and those not receiving IL-1 blockers.
- The publication results showed a dramatic response to anakinra where, in total, only one patient failed to respond (Neel et al 2014, Rossi Semerano et al 2015).
- The analysis from Neel et al (2014) was interpreted as so compelling that the authors suggested that use of anakinra could be diagnostic, and that treatment failure might be indicative of an incorrect diagnosis.
- There were some adverse events, Neel et al 2014, however the participant age was high and the adverse events were mostly in people with pre-existing conditions (dementia, pre-cancer) so should be considered in this context.
- To summarise, anakinra appears to be effective in treating Schnitzler's syndrome.

### **TRAPS**

- The evidence from four papers contributed to the review of anakinra in the treatment of TRAPS.
- The papers included:
  - one prospective cohort study (Gattorno et al 2008), and
  - three retrospective evaluations of a range of periodic fever and autoinflammatory disorders and outcomes from non-IL-1 blockers and with IL-1 blockers (Ozen et al 2017, Ter Haar et al 2013, Rossi-Semerano et al 2016).

- The studies varyingly considered response to treatment by assessing disease activity, response using clinical and inflammatory markers; associated symptoms, duration of attacks, and safety.
- Two papers identified cohorts reflecting both the low penetrance R92Q mutation, and other TRAPS mutations (Ozen et al 2017, Ter Haar et al 2013).
  - All four studies all showed a response to anakinra in the treatment of TRAPS (Gattorno et al 2008, Ozen et al 2017, Ter Haar et al 2013, Rossi-Semerano et al 2016).
- Of particular note was the cohort of five people which showed a relapse when treatment was stopped and improvement when treatment restarted (Gattorno et al 2008).
- Ter Haar et al (2013) reflected that the R92Q mutation responded better to colchicine and NSAIDs than to anakinra unlike the other genetic forms of TRAPS which had a better response to anakinra; however the data for this were not presented in the publication in detail. The publications report injection site reactions but the full extent of AEs was often not reported in detail. However, Rossi-Semerano et al (2015) provide detail on adverse events identifying that injection site pain and liver toxicity are more frequent in children receiving anakinra, overall (not just for TRAPS).
- To summarise, anakinra appears to be effective for inadequately controlled TRAPS, although the benefit may be less for patients with the R92Q mutation.

## 8 Proposed Criteria for Commissioning

### Patient eligibility criteria

#### FMF

- Anakinra may be used in patients who have: documented evidence of ongoing attacks characterised by intense bouts of debilitating abdominal and chest pain that can last 12 to 72 hours; **AND** documented evidence of intolerance due to side effects or of disease unresponsive to effective doses of colchicine up to 3.0 mg/day (or equivalent paediatric age/ weight adjusted dosing regimen)



## **HIDS/MKD**

- Anakinra may be used in patients who have documented evidence of at least three HIDS flares in a six-month period when not receiving treatment, and whose disease is poorly managed by first line treatments or who have documented significant adverse effects associated with first line treatments, provided that there is documented evidence of chronic or recurrent disease activity supported by substantially elevated acute phase markers (CRP and/or SAA)

## **Schnitzler's syndrome**

- Anakinra may be used as a first line treatment in patients with a documented diagnosis of Schnitzler syndrome.

## **TRAPS**

- Anakinra may be used in patients who have severe flares, rash and tissue pain, periorbital edema and joint pain and whose disease is poorly managed by first line treatments or who have documented significant adverse effects associated with first line treatments, provided that there is documented evidence of chronic or recurrent disease activity supported by substantially elevated acute phase markers (CRP and/or SAA).

## **Dosing guidance**

Expert opinion suggests a usual dose of 100mg in adults and children over 40kg, up to a **maximum** daily dose of 10 mg/kg/day in children and 300 mg in adults.

Patients usually receive the drug continuously on the basis that they are always at risk of ongoing systemic inflammation including in between clinical exacerbations; this can lead to amyloidosis and renal failure.

## **Stopping criteria**

The stopping criteria for all the four diseases are:

- Inadequate clinical response to treatment
- Adverse effects, including neutropenia; these may be managed by varying

the dose or occasionally temporarily discontinuing the drug

Patients who have a moderate response should continue for six months. If, at the end of that period the disease response achieved is below the threshold of moderate response, the treatment should be stopped.

A moderate response is defined as an improvement in inflammatory disease activity equating to less than 50% improvement based on the blood markers of inflammation.

## 9 Proposed Patient Pathway

There will be a commissioning plan to make sure this disease is managed within specialist centres that ideally are members or affiliate members of the Rare Immunodeficiency, Autoinflammatory and Autoimmune Disease Network (RITA) European Reference Network (ERN) and have the expertise to manage these complex conditions. This is expected to be no more than 7 providers in England. Patients who are stable on treatment may be managed locally through a shared care arrangement.

## 10 Proposed Governance Arrangements

These are off label uses of anakinra and therefore any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics Committee (or similar) and NHS England may ask for assurance of this process. Provider organisations must register all patients using appropriate software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

## 11 Proposed Mechanism for Funding

The proposed mechanism for funding is via a Trust invoice to the specialised commissioning service.

## **12 Proposed Audit Requirements**

The services will develop a standard data set of biochemical markers and attack frequency and use a standard monitoring system to collate this for standard clinical audit processes. Services will meet annually to share and review outcomes based on the agreed data collection. Patient representatives and commissioners will be invited to this audit day.

## **13 Documents That Have Informed This Policy Proposition**

The publications reviewed informed the policy propositions, see reference list section 15.

## **14 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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