Clinical commissioning policy
Canakinumab for patients with Still's disease refractory to anakinra and tocilizumab (adults and children 2 years and over) 2002

Commissioning position

Summary

Canakinumab is not 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.

The policy is restricted to certain age groups to reflect the marketing authorisation of canakinumab.

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

Still's disease is the umbrella term for two conditions: systemic-onset juvenile idiopathic arthritis (or SJIA) and adult-onset Still's disease (or AOSD). These are rare, inflammatory conditions that can occur at any age, though they have historically been known as two different disease names until relatively recently. Patients will often have symptoms of fever, joint pain, rash, weight loss and muscle aches.

Patients that are diagnosed with one of these conditions are usually started on non-steroidal anti-inflammatory drugs such as ibuprofen to help control symptoms along with steroids. If these drugs do not work, then disease-modifying anti-rheumatic drugs can also be added in. If these drugs do not work, then there are two biologic-type medicines that can be used.

There are a small number of patients where none of these treatments will be effective. This policy proposes the use of canakinumab, another biologic-type medicine to be used for these patients where all other treatments have failed.

What we have decided

NHS England has carefully reviewed the evidence to treat patients with still's disease with canakinumab. NHS England recognises that the published evidence identifies that, at present, there is sufficient evidence to commission this treatment. However, following the relative prioritisation process undertaken in May 2024 , NHS England has concluded that, balanced against other relative priorities that were also considered during this process, canakinumab for patients with still's disease refractory to anakinra and tocilizumab (adults and children 2 years and over) will not be funded within the resources available.

Links and updates to other policies

The policy is for the use of canakinumab in patients with Still's disease who are refractory to treatment with, or do not tolerate corticosteroids, DMARDs, anakinra and tocilizumab. The following policies detail the criteria required for the use of treatments prior to canakinumab:

- NICE TA685: Anakinra for treating Still's disease (2021)
- NHS England 210801P: Tocilizumab for the treatment of AOSD (2018)
- NHS England E03X04: Biologic therapies for the treatment of JIA (2015)
- NICE TA238: Tocilizumab for the treatment of SJIA (2011)

Committee discussion

The Panel debated the evidence base and considered it was reflected by the policy.

The Clinical Priorities Advisory Group considered the evidence and the policy. See the committee papers (link) for full details.

The condition

Still's disease is the overarching name for two conditions: SJIA and AOSD. These two conditions are considered a disease continuum, with onset in childhood or adulthood respectively.

Still's disease is a rare, multisystem autoinflammatory disorder of unknown aetiology, though interleukin-1 (IL-1) and interleukin-6 (IL-6) are thought to have a central role in the disease pathogenesis. Patients typically present with symptoms of fever, polyarthritis, lymphadenopathy and rash. Typically, markers of inflammation are elevated. Other symptoms can include hepatosplenomegaly, serositis, weight loss, myalgia and pericarditis.

Systemic-onset juvenile idiopathic arthritis
SJIA is a severe subtype of juvenile idiopathic arthritis (JIA), making up around 10% of JIA cases. Around one third of patients with SJIA show a monophasic course, with resolution of all symptoms and no recurrences. The remaining patients develop recurring or ongoing symptoms with systemic inflammation.

Some patients can develop macrophage activation syndrome (MAS), a severe, potentially life-threatening complication which is characterised by excessive activation of differentiated macrophages causing fever, lymphadenopathy, hepatosplenomegaly, cytopaenia, liver disease, disseminated intravascular coagulation and neurological involvement. Good disease control is thought to reduce the risk of macrophage activation syndrome. MAS is often treated with anakinra.

Adult-onset Still's disease
Still's disease that presents in adulthood is typically referred to as AOSD. Various diagnostic criteria for AOSD have been developed, but the Yamaguchi classification for AOSD (Yamaguchi et al. 1992) are most frequently used. There are two phenotypes of AOSD, which are recognised according to the predominant symptoms:

- Systemic form of acute-severe onset with fevers, weight loss and significant malaise
- Arthritis-predominant form, which typically has a more indolent onset.

In patients with the systemic form, the course of the disease could be monocyclic (which is usually self-limiting), intermittent or polycyclic. It is estimated that around 30% of cases are monocyclic, 30% are intermittent and 40% are polycyclic. The arthritis-predominant form has less well-defined systemic symptoms and a subset of patients develop a chronic erosive arthritis.

Current treatments

The first line treatment for Still's disease consists of non-steroidal anti-inflammatory drugs (NSAIDs), with corticosteroids if required. If symptoms are not controlled by NSAIDs and corticosteroids, a disease-modifying antirheumatic drug (DMARD) such as methotrexate can be added. Tocilizumab or anakinra can be used for patients that have no response to or do not tolerate DMARDs. Table 1 details the current treatment recommendations.

	SJIA	**AOSD**	
First line	NSAIDs +/- corticosteroids † ‡ §		
Second line	DMARD (methotrexate) §	DMARDs (at least two) † ‡	
Third line	Tocilizumab or anakinra (if not previously used to treat MAS) ¥ §	**Polyarticular AOSD** Tocilizumab ‡ then anakinra † if no response	**Refractory AOSD** Anakinra † then tocilizumab ‡ if no response

Table 1: Current treatment pathways for patients with SJIA, polyarticular AOSD or refractory AOSD. † Information from NICE TA685. ‡ Information from NHS England 170056P. ¥ Information from NHS England E03X04. § Information from NICE TA238.

Proposed treatments

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.

Canakinumab is a recombinant human monoclonal antibody that selectively inhibits the binding of IL-1β to its receptor. This is thought to reduce the effect of IL-1, which is thought to be central in the pathogenesis of Still's disease. Canakinumab is delivered subcutaneously every four weeks.

Epidemiology and needs assessment

SJIA is estimated to account for 10-20% of all JIA patients, which has a yearly incidence between 1.6 and 23 new cases per 100,000 children. Though it is recognised that the percentage of children with SJIA may be increased in other populations, for example in parts of Asia it is thought to account for up to 30-40% of all JIA cases (Orpha.net, 2020). It is estimated that there around 10,000 children with JIA at any one time in the UK, with around 10% of children diagnosed with JIA having SJIA (NICE ESNM36, 2014), which means there are around 1,000 children with SJIA at any one time in the UK.

AOSD has an estimated annual incidence of approximately 0.22/100,000 in Japan (Wakai et al. 1997), 0.16/100,000 in France (Magadur-Joly et al. 1995) and 0.4/100,000 in northern Norway (Evensen et al. 2006). No estimates exist for an England population. The point prevalence of AOSD in the northern Norway population was estimated between 3.4-6.9/100,000, though this

is thought to be higher than in France or Japan. Assuming the English population is similar to that of the French population there would be 90 new cases of AOSD per year in England. Extrapolating the point prevalence from the Norwegian population would estimate around 1,900 patients with AOSD.

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. 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). Assuming the SJIA population is around half that of the adult population with AOSD, it is estimated that around 22 patients would be eligible for treatment with canakinumab each year.

Evidence summary

Two independent evidence reviews were conducted for the use of canakinumab in patients with SJIA and patients with AOSD. The evidence reviews can be accessed on the NHS England website.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Biologic-type medicine	A substance that is made from a living organism or its products and is used in the prevention, diagnosis or treatment of disease. Biologic agents include antibodies, interleukins and vaccines.
Corticosteroids	A group of natural and synthetic analogues of the hormones secreted by the hypothalamic-anterior pituitary-adrenocortical (HPA) axis, more commonly referred to as the pituitary gland.
Disease-modifying anti-rheumatic drug	A group of medications commonly used in patients with rheumatoid arthritis. They work to slow down disease progression and include drugs such as azathioprine, ciclosporin, leflunomide, methotrexate and mycophenolate mofetil. These agents also commonly referred to as immunosuppressive therapies are widely used in a variety of other inflammatory conditions.
Interleukins	A group of cytokines which are synthesised by lymphocytes, monocytes, macrophages and certain other cells. They function mostly in the 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 despite treatment.