NHS ENGLAND SPECIALISED COMMISSIONING – RESPONSE TO AMENDMENTS REQUESTED TO EVIDENCE REVIEW DURING ENGAGEMENT OR CONSULTATION

URN	1924
POLICY TITLE	Anakinra for Haemophagocytic Lymphohistiocytosis (HLH) for adults and children in all ages
CRG:	Specialised Rheumatology
NPOC:	Internal Medicine
Date	21/04/2021

Description of comments during consultation (If studies have been suggested please provide a list of references)	i. Minoia F, Davì S, Horne A, et al. Clinical Features, Treatment, and Outcome of Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A Multinational, Multicenter Study of 362 Patients: Macrophage Activation Syndrome in Systemic JIA. Arthritis Rheumatol 2014; 66: 3160–9 ii. Miettunen PM, Narendran A, Jayanthan A, Behrens EM, Cron RQ. Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients. Rheumatology 2011; 50: 417–9 The above articles included within the stakeholder consultation were selected for public health review by the Policy Clinical Lead.
Action taken by Public Health lead	The full text articles were retrieved through the PHE Library Service, reviewed and summarised as follows: Miettunen PM, Narendran A, Jayanthan A et al. Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients. Rheumatology 2011;50:417–419. Macrophage activation syndrome MAS is a severe complication of paediatric inflammatory diseases with mortality rates up to 53%. Its early recognition

	and treatment are critical in improving outcome. All patients at the Alberta Children's Hospital and the Children's Hospital of Philadelphia, who received anakinra between 2006 and 2009 for prMAS were studied retrospectively. When prMAS occurred, all 12 patients initially received corticosteroids (n=12) and other immunosuppressants [IVIG (n=9), ciclosporin (n¼=10), etoposide (n=2, one dose each) and etanercept (n=1)] with limited benefit. Anakinra was given for better prMAS control. Etanercept and etoposide were discontinued when anakinra was initiated. In all other patients, anakinra was added to pre-existing MAS therapy at 2 mg/kg/day s.c. (maximum dose 100 mg/day) once daily. Before anakinra, five patients required intensive care, and potential infectious triggers were present in seven patients. All patients met diagnostic criteria for Ravelli's sJIA-associated MAS. The median hospitalization stay before anakinra was 11 days. All patients achieved MAS remission after addition of anakinra within a median of 13 days. Corticosteroids were discontinued by 6 weeks in seven patients. Of all laboratory parameters, CRP and ferritin correlated the best with MAS activity. CRP levels were drastically reduced after the use of Anakinra from 168 to 6.8 mg/L, 5 days after Anakinra. The clinical response was dramatic and rapid, occurring within days. All patients fully recovered, including five who had required intensive care support. The excellent outcome in MAS patients was attributed to early diagnosis and immediate therapeutic intervention, including early use of anakinra. As all patients were treatedwith anakinra and traditional therapies, it is possible that the combination of medications contributed to the resolution of MAS. It was therefore recommended that anakinra was used in combination with high-dose corticosteroids, ciclosporin and IVIG, rather than as a sole agent. Further studies with larger patient numbers are required to better define the promising role of Anakinra in the management of prMAS. Minoia F, Davi S, Horne A et al. Clinical Features, Treatment, and Outcome of Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis. Arthritis & Rheumatology Vol. 66, No. 11, November 2014, pp 3160–3169.

	In this multinational, multicentre study, 95 paediatric rheumatologists and haemato-oncologists from 33 countries entered patient data collected retrospectively into a web-based database. The purpose of the study was to describe the clinical, laboratory, and histopathologic features, therapeutic interventions, and outcome of the 362 patients enrolled in the survey. A total of 362 patients, 22% of whom had MAS at the onset of systemic JIA. The median age at onset of systemic JIA was 5.3 years, and the median duration of systemic JIA at MAS onset was 3.5 months. MAS was reported to occur most frequently (51.7%) in the setting of active systemic JIA or during a systemic JIA flare. An infectious trigger was detected in 34.1% of the patients. The most frequent clinical manifestations were fever (96%), hepatomegaly (70%), and splenomegaly (58%). Central nervous system dysfunction and haemorrhagic manifestations (bleeding and DIC) were recorded in 35% and 20% of the patients. At MAS onset, platelet count and levels of liver transaminases, ferritin, lactate dehydrogenase, triglycerides, ESR, CRP, haemoglobin, and D-dimer were abnormal in 50% of the patients -Platelet count and liver transaminase, ferritin, lactate dehydrogenase, triglyceride, and D-dimer levels were the sole laboratory biomarkers showing a percentage change of >50% between the pre-MAS visit and MAS onset. Evidence of macrophage haemophagocytosis was found in 60% of the patients who underwent bone -marrow aspiration. At the time of full-blown MAS, only levels of liver transaminases, ferritin, lactate dehydrogenase, triglycerides, D-dimer, haemoglobin, and CRP were abnormal in 90% of the patients. Almost all patients (97.7%) had received corticosteroids, most often I.V. Cyclosporine was administered to approximately two-thirds of the patients (61.2%) and intravenous immunoglobulin to approximately one third of the patients (36.3%). Only 15.2% of the patients were treated with biologic agents, with anakinra being the most commonly selected agent (9.7%). Of the 33 patients who received anakinra, 93.9% were seen after 2006 and 63.6% were seen after 2008.

	Etoposide was given in 11.8 % of patients and prescribed more frequently by haemato-oncologists (18.4%) than by rheumatologists (9.9%). Patients who received etoposide had a greater frequency of haemorrhagic manifestations, CNS dysfunction, and pulmonary and renal involvement. Notably, patients who received etoposide had more severe disease manifestations and were more likely to be admitted to the ICU than those who did not. During the timeframe of patient inclusion (2002–2012), there were some variations in the treatment approach to MAS, with patients seen in the earlier years being more likely to have received corticosteroids with or without cyclosporine and those treated in more recent years being more likely to have received biologic agents or etoposide. Outcome data showed that 34.9% of the patients required ICU admission, and 8.1% died as a consequence of MAS. Comment- Both articles fulfil the PICO criteria and time frame but were probably excluded because of one being a retrospective narrative review and the second included as a letter to the Editor. They complement and endorse the policy proposition but do not materially change it.
Outcome for studies suggested during consultation	
1. Evidence already identified during the evidence review	NA
2.New evidence identified by stakeholders that does not fall within PICO and search methodology	NA
3.New evidence identified by stakeholders that falls within PICO and search methodology but does not materially affect the conclusions of the existing evidence review	Both articles fulfil the PICO criteria and time frame but were probably excluded because of one being a retrospective narrative review and the second included as a letter to the Editor. They complement and endorse the policy proposition but do not materially change it.

4.New evidence identified by stakeholders that falls within PICO and search methodology, that does materially affect the conclusions of the existing evidence review. Updated evidence review to be undertaken (agreed with CET)	NA