CLINICAL PRIORITIES ADVISORY GROUP
7 July 2021

Agenda Item No	2.1
National Programme	Internal Medicine
Clinical Reference Group	Specialised Rheumatology
URN	1924

Title
Anakinra for Haemophagocytic Lymphohistiocytosis (HLH) for adults and children in all ages

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
For routine commissioning: The proposition is for Anakinra to be routinely commissioned as a treatment for adults and children in all ages for Haemophagocytic lymphohistiocytosis (HLH) within the criteria set out in the policy. HLH happens when the body's immune system responds abnormally to illness or some treatments which target the immune system. Anakinra, when given early, stabilises the hyperinflammatory condition HLH and is usually a bridging treatment to allow diagnosis and treatment of the underlying triggering disease. When it occurs acutely it usually results in admission to critical care but only sometimes requires longer term treatment with Anakinra. The proposal is cost saving as it reduces the need to use intravenous immunoglobulin (IVig) as a treatment which is the current treatment for HLH.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report and an additional evidence report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In adults and children with haemophagocytic lymphohistiocytosis (HLH), what is the clinical effectiveness and safety of anakinra compared with standard treatment?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
In hospital and 30-day mortality **Certainty of evidence:** Very Low	Mortality is relevant to patients because HLH is a serious, potentially life-threatening condition. In total, five studies (one comparative cohort analysis using data from a randomised controlled trial (Opal et al 1997) and four case series) provided evidence relating to in hospital and 30-day mortality. Mortality was reported at 28 days in the comparative cohort study. In hospital mortality was reported by the four case series (timepoints not defined). The comparative cohort study compared results for anakinra and placebo in adults with features of macrophage activation syndrome (MAS) with presence of hepatobiliary dysfunction and disseminated intravascular coagulation. The four case series reported non-comparative results for people who were treated with anakinra for HLH.

Outcome	Evidence statement
	At 28 days • 1 comparative cohort study (Shakhoory et al 2016) (n=43) showed *statistically significant lower* mortality in patients treated with anakinra compared to placebo (34.6% vs 64.7%, p=0.0006) with a lower risk of death (hazard ratio (HR) 0.28 (95%CI 0.11 to 0.71), p=0.0071. (**VERY LOW)** In hospital Four case series reported the numbers and proportion of patients treated with anakinra who did not survive to hospital discharge. • 1 case series (Eloseily et al 2019) (n=44) provided non-comparative evidence that 12/44 (27%) patients treated with anakinra did not survive to hospital discharge[1]. (**VERY LOW)** • 1 case series (Gregory et al 2019) (n=16), provided non-comparative evidence that 5/16 (31%) patients treated with anakinra did not survive to hospital discharge. (**VERY LOW)** • 1 case series (Wohlfarth et al 2019) (n=8), provided non-comparative evidence that 4/8 (50%) patients treated with anakinra did not survive to hospital discharge. (**VERY LOW)** • 1 case series (Kumar et al 2017) (n=13), provided non-comparative evidence that 4/13 (31%) patients treated with anakinra did not survive to hospital discharge. (**VERY LOW)** **These studies provided very low certainty evidence that compared to standard treatment, anakinra reduces 30-day mortality in patients with HLH. In patients receiving anakinra for HLH, in hospital mortality was between 27% and 50%.**
Intensive care unit (ICU) duration of stay **Certainty of evidence: Very low**	Duration of stay in ICU is relevant to patients because HLH is a serious, potentially life-threatening condition. Longer stays in ICU can impact on survival, longer term outcomes and quality of life for the patient, and resource utilisation for health services. One case series provided evidence relating to ICU length of stay. The case series reported non-comparative results for people who were treated with anakinra for HLH. • 1 case series (Wohlfarth et al 2019) (n=8) provided non-comparative evidence that for all patients treated with anakinra, the mean length of stay was 36[2] days (range 3 to 118 days). For the 5/8 (63%) patients who were discharged from ICU, the mean length of stay was 43.6 days (range 6 to 118 days). (**VERY LOW)** **This study provided no evidence about ICU duration of stay for patients with HLH treated with anakinra compared to**

[1] Although not explicitly stated, the reviewers have assumed that the deaths were in hospital; 9/12 deaths were recorded to be due to septic shock and/or multiorgan system failure (MOSF), the other 3/12 causes of death included fungal infection.

[2] The narrative in the publication states 15 days but this is not consistent with the results published in table 2 (Wohlfarth et al 2019)

Outcome	Evidence statement
	standard treatment. In patients receiving anakinra for HLH, duration of ICU stay ranged from 3 to 118 days.
Important outcomes	
Abolition of fever **Certainty of evidence:** Very low	Abolition of fever or defervescence is relevant to patients because it is an indication of reduced HLH. In total, two case series provided evidence relating to the time taken to reduce or abolish fever after the introduction of anakinra. These case series reported non-comparative results for people who were treated with anakinra for HLH. • 1 case series (Eloseily et al 2019) (n=44) provided non-comparative evidence that for all patients treated with anakinra, the mean time for defervescence was 1.7 (standard deviation (SD)±1.11) days. For patients who survived, the mean time for defervescence was 1.6 (SD±1.0) days whereas for those who died the mean time for defervescence was 2.0 (SD±1.4) days. (**VERY LOW)** • 1 case series (Sonmez et al 2018) (n=15) provided non-comparative evidence that the resolution time of fever after the introduction of anakinra was a median of 2 (range 1 to 4) days. (**VERY LOW)** **These studies provide no evidence about the abolition of fever with anakinra compared to standard treatment in patients with HLH. In patients receiving anakinra for HLH, time to abolition of fever was approximately 2 days.**
Hyperferritinaemia – reduction in serum ferritin levels of 20-50% or more **Certainty of evidence:** Very low	A reduction in serum ferritin levels of 20-50% or more is relevant to patients because it is an important marker of improvement in disease activity in patients who are critically ill with HLH. In total, two case series provided evidence relating to ferritin levels after initiation of treatment with anakinra. These case series reported non-comparative results for people who were treated with anakinra for HLH. • 1 case series (Eloseily et al 2019) (n=44) provided non-comparative evidence that <u>within</u> 15 days of treatment initiation with anakinra, the ferritin level (mean±SD) was 14,435 ± 79,842 ng/mL compared to a baseline level of 33,316 ± 56,514 ng/mL(reported to be a 57% decrease). <u>At</u> 15 days after treatment initiation, the mean change was 19,256 (SD 66,334) ng/mL corresponding to a mean decrease of 72(SD 62)%. (**VERY LOW)** • 1 case series (Wohlfarth et al 2019) (n=8) provided non-comparative evidence for this outcome for 7 out of 8 patients in the study. The median ferritin level 14 days after treatment initiation with anakinra was 2,754 (489-9036) µg/L compared to the median baseline for all 8 patients of 32,419 (946-79,586) µg/L. No statistical analysis was performed due to the

Outcome	Evidence statement
	small sample size and the loss to follow up of one patient. (**VERY LOW)** **These studies provide no evidence about reduction in serum ferritin levels of 20-50% with anakinra compared to standard treatment or more in patients with HLH. In patients receiving anakinra for HLH, ferritin levels reduced from baseline within approximately 15 days after treatment.**
Length of hospital stay **Certainty of evidence:** Very low	Length of stay in hospital is relevant to patients because HLH is a serious, potentially life-threatening condition which may be associated with long length of stay. This can impact on survival, quality of life for the patient, and resource utilisation for health services. In total, three case series provided evidence relating to length of hospital stay. The case series reported non-comparative results for people who were treated with anakinra for HLH. • 1 case series (Eloseily et al 2019) (n=44) provided non-comparative evidence that for all patients treated with anakinra, the mean (±SD) duration of hospitalisation was 30[3] (±40) days. For patients who survived (n=32), the duration of hospitalisation was 18 (±16) days whereas for those who died (n=12), it was statistically significantly longer 62.0 (±62) days, p=0.0005. (**VERY LOW)** • 1 case series (Sonmez et al 2018) (n=15) provided non-comparative evidence that the time of discharge after anakinra initiation was a median of 12 (range 8 to 21) days. (**VERY LOW)** • 1 case series (Wohlfarth et al 2019) (n=8) provided non-comparative evidence that for all patients treated with anakinra, the mean length of stay was 65.75 days (range 5 to 190 days). For the 4/8 (50%) patients who were discharged from hospital, the mean length of stay was 99.25 days (range 32 to 190 days). (**VERY LOW)** **These studies provide no evidence about length of hospital stay with anakinra compared to standard treatment in patients with HLH. In patients receiving anakinra for HLH, length of hospital stay ranged from an average of approximately 12 to 66 days.**
Use or change in dose of intravenous immunoglobulin (IVIG)	Use of or change in dose of IVIG is relevant to patients because IVIG may be used (usually with steroids) to reduce inflammation and suppress the immune system. A reduction or cessation in IVIG use is an indication that the severe inflammation responsible for the life-threatening symptoms associated with HLH has been resolved.

[3] although the narrative abstract of the published study states that the median duration of hospitalisation was 15 days.

Outcome	Evidence statement
Certainty of evidence: N/A	**No evidence was identified for this outcome.**
Use or change in dose of steroids **Certainty of evidence:** Very low	Use of or change in dose of steroids is relevant to patients because steroids are drugs that can reduce inflammation and suppress the immune system. A reduction or cessation in steroid use is an indication that the severe inflammation responsible for the life-threatening symptoms associated with HLH has been resolved. One case series provided evidence relating to use or change in dose of steroid. The case series reported non-comparative results for people who were treated with anakinra for HLH. • 1 case series (Sonmez et al 2018) (n=15) provided non-comparative evidence that the median cessation time of steroids after anakinra initiation was 10 (range 4 to 13) weeks. (**VERY LOW)** **This study provides no evidence on the use or change in dose of steroid medication with anakinra compared to standard treatment in patients with HLH. In patients receiving anakinra for HLH, median time to cessation of steroids was 10 weeks.**
Use or change in dose of etoposide **Certainty of evidence:** N/A	Use of or change in dose of etoposide is relevant to patients because etoposide is a chemotherapy known to be effective against HLH. A reduction or cessation in etoposide use is an indication that the severe inflammation responsible for the life-threatening symptoms associated with HLH has been resolved. **No evidence was identified for this outcome.**
Use or change in dose of ciclosporin **Certainty of evidence:** N/A	Use of or change in dose of ciclosporin is relevant to patients because cyclosporine may be used (in combination with steroids with or without IVIG) to suppress the cell-mediated immune reactions. A reduction or cessation in ciclosporin use is an indication that the life-threatening symptoms associated with HLH have been resolved. **No evidence was identified for this outcome.**
Safety	
Critical outcomes	
Acquired Infection **Certainty of evidence:** Very low	Acquired infection is relevant to patients because it can affect survival, quality of life, length of stay and longer-term outcomes. One case series provided evidence relating to acquired infection after the introduction of anakinra. The case series reported non-

Outcome	Evidence statement
	comparative results for people who were treated with anakinra for secondary haemophagocytic lymphohistiocytosis (sHLH)/MAS. • 1 case series (Eloseily et al 2019) (n=44) provided non-comparative evidence that 6/12 (50%) patients who died had systemic infections (5 had positive fungal cultures). The authors stated that *'there was no association with the timing of anakinra administration and infection.'* (**VERY LOW)** **This study provided no evidence about acquired infection for patients with HLH treated with anakinra compared to standard treatment. In patients receiving anakinra for HLH, half of the patients who died had a systemic infection.**
Adverse events **Certainty of evidence:** Very low	Adverse events are relevant to patients because they may affect survival, require additional treatments, and reduce quality of life. Serious adverse events may negate the expected health improvement associated with treatment. Two case series provided evidence relating to adverse events after the introduction of anakinra. The case series reported non-comparative results for people who were treated with anakinra for sHLH/MAS. • 1 case series (Sonmez et al 2018) (n=15) provided non-comparative evidence that no patients experienced severe injection site reactions. One patient developed vitiligo causing the cessation of treatment with anakinra (timepoint not reported). (**VERY LOW)** • 1 case series (Wohlfarth et al 2019) (n=8) provided non-comparative narrative evidence that no patients experienced *'unscheduled treatment discontinuations or adverse events considered attributable to the administration of anakinra'*. *No overt treatment toxicity was reported.* (**VERY LOW)** **These studies provide no evidence about adverse events with anakinra compared to standard treatment in patients with HLH. The number of adverse events reported with anakinra was low.**
Important outcomes	
Complications – multiorgan failure, severe cognitive impairment, learning disabilities, nerve paresis, renal impairment and obstructive bronchiolitis etc.	Complications caused by treatment with anakinra are relevant to patients because they could negatively impact treatment outcomes, particularly those that might persist after the episode of HLH has been resolved. **No evidence was identified for this outcome.**

Outcome	Evidence statement
Certainty of evidence: N/A	
Abbreviations: HLH - haemophagocytic lymphohistiocytosis, HR – hazard ratio, ICU - intensive care unit, IVIG - intravenous immunoglobulin, MAS - macrophage activation syndrome, MOSF - multiorgan system failure, µg/L – micrograms per litre, ng/mL – nanograms per millilitre, SD - standard deviation, sHLH - secondary haemophagocytic lymphohistiocytosis.	

In adults and children with HLH, what is the cost effectiveness of anakinra compared with standard treatment?

Outcome	Evidence statement
Cost Effectiveness	No evidence was identified for cost effectiveness

From the evidence selected is there any data to suggest that there are subgroups of patients that may benefit from treatment with anakinra more than the wider population of interest?

Outcome	Evidence statement
Predictors of decreased mortality rate **Certainty of evidence:** Very low	One case series (Eloseily et al 2019) (n=44) provided non-comparative evidence that for patients with sHLH/MAS treated with anakinra, there was a decreased mortality rate in two groups: • Patients who received anakinra earlier (≤5 days of hospitalisation) compared to those who received anakinra after 5 days of hospitalisation had a *statistically significant decreased mortality rate* (p=0.046) and a *greater drop in ferritin level* (p=0.001) • The survival rate in patients with rheumatic/autoimmune diseases was 86% (100% for systemic juvenile idiopathic arthritis (sJIA) and 70% for systemic lupus erythematosus (SLE) and related conditions), compared to 50% for all other patients with sHLH. Patients with an underlying diagnosis of sJIA had a *statistically significant lower rate of mortality* (p=0.006) compared to those with other underlying conditions. (**VERY LOW)**
Abbreviations: MAS - macrophage activation syndrome, sHLH - secondary haemophagocytic lymphohistiocytosis, sJIA - systemic juvenile idiopathic arthritis, SLE - systemic lupus erythematosus.	

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** Patients have severe problems in walking about or are unable to walk • **ability to provide self-care:** Patients have severe problems in washing or dressing or are unable to wash or dress • **undertaking usual activities:** Patients have severe problems in doing their usual activities or are unable to do their daily activities • **experience of pain/discomfort:** Patients can have moderate pain or discomfort • **experience of anxiety/depression:** Patients are severely anxious or depressed
Further details of impact upon patients: HLH is a life-threatening condition and may present slowly or suddenly with symptoms related to multiorgan failure including fever, seizures, and weakness Symptoms are fever, coughing and trouble breathing, stomach ache, vomiting, and diarrhoea, nervous system problems such as headaches, trouble walking, vision disturbances, seizures, cognitive impairment and weakness. When HLH occurs suddenly it can be a traumatic experience for patients and their families. **Further details of impact upon carers:** There is a high burden on caregivers in supporting patients with daily tasks of living and particularly following sudden onset HLH due to reduced ability to self-care and disability. If there is genetic cause of HLH then related carers will need genetic counselling and testing as well as resulting in additional anxiety. Treatment of HLH may require other additional intensive treatments providing a burden on carers.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This Clinical Commissioning Policy Proposition recommends anakinra for the treatment of Haemophagocytic Lymphohistiocytosis. This is an off-label use of anakinra which is excluded from tariff. It is licensed for some indications in children and infants aged 8 months and older with a body weight of 10 kg or above. No data is available for children below this age or weight.

Considerations from review by National Programme of Care
The NPoC noted the significant impact on patients with HLH which is the focus of this policy proposition. The proposition received the full support of the Internal

Medicine NPoC Assurance Group in May 2021. The NPoC noted the management of rare rheumatological conditions are predominantly provided through Specialised Rheumatology adult and children's services, however a smaller number have a specific interest in HLH. It was recommended commissioners will work with regional networks to confirm local pathways for adults and children. The proposal is cost saving as it reduces the need to use IVIg treatment which is the current treatment for HLH.