NHS England

Evidence review: Anakinra for Haemophagocytic Lymphohistiocytosis

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Evidence review: Intervention for indication

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Contents

1. Introduction

This review examines the clinical effectiveness, safety and cost effectiveness of anakinra compared to current standard treatment including corticosteroids, intravenous immunoglobulin (IVIG), ciclosporin, methotrexate and/or etoposide in people presenting with primary or secondary haemophagocytic lymphohistiocytosis (HLH).[1]

2. Executive summary of the review

Six papers were included in this review (Eloseily et al 2019, Gregory et al 2019, Kumar et al 2017, Shakoory et al 2016, Sonmez et al 2018 and Wohlfarth et al 2019).

The paper by Shakhoory et al (2016) was a comparative cohort study based on a subgroup analysis of adults recruited to an earlier phase III randomised controlled trial (RCT) (Opal et al 1997)[2]. The other five papers were single centre, retrospective case series of paediatric patients (Eloseily et al 2019, Gregory et al 2019, Sonmez et al 2018) and adults (Kumar et al 2017, Wohlfarth et al 2019). None of these studies were undertaken in the UK.

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

Critical Outcomes. The critical outcomes for decision making are in hospital and 30-day mortality and intensive care unit (ICU) duration of stay. Acquired infection and adverse events are also critical outcomes. These are reported in the question on safety below. Certainty in the quality of the evidence for the critical outcomes was very low when assessed using modified GRADE.

In hospital and 30-day mortality
In total, five studies (one comparative cohort analysis using subgroup data from an earlier RCT (Opal et al 1997) and four case series) provided evidence relating to in hospital and 30-day mortality.

For adults with macrophage activation syndrome (MAS - defined as the presence of hepatobiliary dysfunction (HBD) and disseminated intravascular coagulation (DIC)), one comparative cohort analysis (n=43) reported statistically significantly lower 28-day mortality in patients treated with anakinra (n=26) compared to placebo (n=17) (34.6% vs 64.7%, p=0.0006) with a lower risk of death (HR 0.28 (95%CI 0.11 to 0.71), p=0.007) (Shakhoory et al 2016). This study provided very low certainty evidence that compared to standard treatment, anakinra reduced 28-day mortality.

In patients receiving anakinra for HLH, in hospital mortality at undefined timepoints reported in four case series (total n=81) ranged from 27% to 50% (Eloseily et al 2019, Gregory et al 2019, Wohlfarth et al 2019, Kumar et al 2017). The certainty of the evidence was very low.

[1] HLH may also referred to as MAS, MALSS, cytokine storm syndrome, cytokine release syndrome, hyperferritinaemia
[2] 763 patients (out of 906 originally recruited) completed the original RCT for anakinra for severe sepsis. This study is an analysis of 43 adults who had hepatobiliary dysfunction/ disseminated intravascular coagulation.

ICU duration of stay
In adults who received anakinra for HLH, non-comparative evidence from one case series (n=8) reported that the mean ICU duration of stay was 36 days (range 3 to 118 days). For the 5/8 (63%) patients who survived to discharge from ICU, the mean length of stay was 43.6 days (range 6 to 118 days). This single centre, case series (Wohlfarth et al 2019) provided no evidence about ICU duration of stay for patients with HLH treated with anakinra compared to standard treatment. The certainty of the evidence was very low.

Important Outcomes. The outcomes important to decision making are abolition of fever, hyperferritinaemia – reduction in serum ferritin levels of 20-50% or more, length of hospital stay, complications such as multiorgan failure, severe cognitive impairment, learning disabilities, nerve paresis, renal impairment and obstructive bronchiolitis, use or change in dose of IVIG, steroids, etoposide or ciclosporin., Complications are reported in the question on safety below. Certainty in the quality of the evidence for the important outcomes was very low when assessed using modified GRADE.

Abolition of fever
In paediatric patients who received anakinra for HLH, non-comparative evidence from two case series (total n=59) reported time to abolition of fever of approximately two days. The mean time for reduction in fever (referred to as defervescence) reported by Eloseily et al 2019 was 1.7 (SD±1.11) days and the median time to resolution of fever reported by Sonmez et al 2018 was 2 (range 1 to 4) days. These studies provide no evidence about the abolition of fever with anakinra compared to standard treatment in patients with HLH. The certainty of the evidence was very low.

Hyperferritinaemia – reduction in serum ferritin levels of 20-50% or more
In patients who received anakinra for HLH, non-comparative evidence from two case series (total n=52) reported a reduction in serum ferritin levels. At 15 days after treatment initiation, one case series (n=44) reported a mean change in ferritin levels of 19,256 (SD 66,334) ng/mL corresponding to a mean decrease of 72% (SD 62) (Eloseily et al 2019).

At 14 days after treatment initiation with anakinra, one case series reported a median ferritin level of 2,754 (489-9036) µg/L for seven patients compared to the median baseline for all eight patients of 32,419 (946-79,586) µg/L (Wohlfarth et al 2019). These studies provide no evidence about reduction in serum ferritin levels of 20 to 50% or more with anakinra compared to standard treatment in patients with HLH. The certainty of the evidence was very low.

Length of hospital stay (LOS)
In patients who received anakinra for HLH, non-comparative evidence from three case series (total n=67) reported length of hospital stay which ranged from an average of approximately 12 to 66 days for all patients. Eloseily et al 2019 reported a mean (±SD) duration of hospitalisation of 30 (±40) days for 44 paediatric patients treated with anakinra. LOS was significantly longer for the 12 patients who did not survive to discharge (62.0 (±62) days) compared to those who survived (18.6 (±16) days, p=0.0005). Conversely, Wohlfarth et al 2019 reported a longer mean LOS for four patients who survived to discharge (99.25 days (range 32 to 190 days) compared to the mean LOS for all 8 adults included in the study (65.75 days (range 5 to 190 days).

Sonmez et al 2018 reported the median time of discharge after anakinra initiation was 12 (range 8 to 21) days (n=15 paediatric patients). These studies provide no evidence about

length of hospital stay with anakinra compared to standard treatment in patients with HLH. The certainty of the evidence was very low.

Use or change in dose of IVIG
No evidence was identified for this outcome.

Use of or change in dose of steroids
In paediatric patients who received anakinra for HLH, non-comparative evidence from one case series (n=15) reported that the median cessation time of steroids after anakinra initiation was 10 (range 4 to 13) weeks (Sonmez et al 2018). 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. The certainty of the evidence was very low.

Use of or change in dose of etoposide
No evidence was identified for this outcome.

Use of or change in dose of ciclosporine
No evidence was identified for this outcome.

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

Acquired infection (Critical for decision making)
In paediatric patients who received anakinra for HLH, non-comparative evidence from one case series (n=44) reported that 6/12 (50%) patients who died had systemic infections (5 had positive fungal cultures) although the authors stated that *'there was no association with the timing of anakinra administration and infection' (*Eloseily et al 2019). This study provided no evidence about acquired infection for patients with HLH treated with anakinra compared to standard treatment. The certainty of the evidence was very low.

Adverse events (Critical for decision making)
In patients who received anakinra for HLH, non-comparative evidence from two case series (total n=23) provided information on adverse events. One patient developed vitiligo causing the cessation of treatment with anakinra (timepoint not reported) (Sonmez et al 2018). Wohlfarth et al 2019 reported no unscheduled treatment discontinuations or adverse events considered attributable to the administration of anakinra. 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. The certainty of the evidence was very low.

Complications (Important for decision making) - multiorgan failure, severe cognitive impairment, learning disabilities, nerve paresis, renal impairment and obstructive bronchiolitis etc

No evidence was identified for this outcome.

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

No cost effectiveness studies were available for inclusion in this review.

From the evidence selected, are there any subgroups of patients that may benefit from anakinra more than the wider population of interest?

One, single centre, case series (Eloseily et al 2019, n=44) identified two subgroups of paediatric patients treated with anakinra for HLH that experienced a lower rate of in hospital mortality. The survival rate in patients with rheumatic/autoimmune diseases was 86% (100% for sJIA and 70% for SLE and related conditions), compared to 50% for all other patients with secondary haemophagocytic lymphohistiocytosis (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. In addition, patients who received anakinra within five days of hospitalisation had a statistically significant decreased mortality rate (p=0.046) (and a greater drop in ferritin level (p=0.001)) compared to those who received anakinra after five days of hospitalisation. The certainty of the evidence was very low.

Limitations. The key limitation to identifying the effectiveness of anakinra compared to standard treatment for HLH is the lack of reliable comparative studies. It should be noted that HLH is a rare condition and therefore conducting prospective comparator studies may be unrealistic. Very low certainty evidence was identified from one comparator study (a retrospective subgroup analysis of patients receiving anakinra or placebo recruited to an RCT published in 1997) and five small, retrospective, single centre case series from countries outside the UK which reported outcomes for patients who were treated with anakinra. There was heterogeneity among the patients included in the studies (variation in diagnostic criteria, severity of disease and underlying disease), along with variation in anakinra and concomitant treatments. The outcomes reported may not be wholly attributable to anakinra. The results from all these studies may not be generalisable to the current NHS practice in England.

Conclusion. The very low certainty evidence from all the studies included in this review is insufficient to draw reliable conclusions about the clinical effectiveness and safety of anakinra compared to standard treatments in patients with HLH. No evidence on the cost effectiveness of anakinra compared to current standard treatments was identified.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In adults and children with HLH, what is the clinical effectiveness of anakinra compared with standard treatment?
2. In adults and children with HLH, what is the safety of anakinra compared with standard treatment?
3. In adults and children with HLH, what is the cost effectiveness of anakinra compared with standard treatment?
4. From the evidence selected, are there any subgroups of patients that may benefit from anakinra more than the wider population of interest?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2019).

The searches for evidence were informed by the PICO document and were conducted on 30th January 2020.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were quality appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Six papers were identified for inclusion (Eloseily et al 2019, Gregory et al 2019, Kumar et al 2017, Shakoory et al 2016, Sonmez et al 2018 and Wohlfarth et al 2019). Table 1 provides a summary of these included studies and full details are given in Appendix E.

The paper by Shakhoory et al (2016) was a comparative cohort study based on a subgroup analysis of an earlier phase III randomised controlled trial (Opal et al 1997). The other five papers were all single centre, retrospective case series.

No cost effectiveness studies suitable for inclusion in this evidence review were identified.

Table 1 Summary of included studies

Study	Population	Intervention and comparator	Outcomes reported

Eloseily et al 2019
 	
Single centre, retrospective case series
 	
Alabama, USA
	44 consecutive paediatric patients with a diagnosis of secondary HLH or MAS	**Intervention**
		Anakinra (dose, frequency of dosing, route of administration, duration of treatment not reported)
		
		Concomitant treatments included:
		• glucocorticoids
		• ciclosporin A
		• IVIG
		• etoposide
		• tocilizumab
		• abatacept
		• rituximab
		• cyclophosphamide
		• plasmapheresis
		
		Comparison
		None
			Critical Outcomes
			• Overall mortality (timepoint not reported)
			• Systemic infection (timepoint not reported)
			
			Important outcomes
			• (Time to) defervescence after anakinra start
			• Ferritin level
			  ○ Within 15 days of start of anakinra
			  ○ Change at 15 days
			  ○ Decrease at 15 days
			• Length of hospitalisation
			
			Other[b]
			• predictive factors correlated with outcomes

Gregory et al 2019 Single centre, retrospective case series Washington DC, USA	16 paediatric patients with a diagnosis of primary or secondary HLH The study included 33 patients. Only data for the 16 patients who received anakinra were extracted for inclusion in this review No subgroups reported	**Intervention** Anakinra (dose, frequency of dosing, route of administration, duration of treatment not reported) Concomitant treatments not reported **Comparison** None	**Critical Outcomes** • Survival to hospital discharge (timepoint not reported) **Important outcomes** • None reported
Kumar et al 2017 Single centre, retrospective case series Iowa, USA	13 adults with a diagnosis of secondary HLH or MAS The study included 19 patients. Only data for the 13 patients who received anakinra were extracted for inclusion in this review	**Intervention** Anakinra 100mg subcutaneously twice daily (duration of	**Critical Outcomes** • Survival to hospital discharge (timepoint not reported) **Important outcomes** • None reported

Study	Population	Intervention and comparator	Outcomes reported
	No subgroups reported	treatment was not reported) Concomitant treatments included: • steroids • ciclosporin A • IVIG • tocilizumab **Comparison** None	
Shakoory et al 2016 Comparative cohort study (subgroup analysis of a prior Phase III RCT by Opal et al 1997) Study location not reported[d]	43 adults with a diagnosis of sepsis with multiorgan dysfunction and /or shock with features of MAS (defined as the presence of hepatobiliary dysfunction/ disseminated intravascular coagulation) [c] No subgroups reported	**Intervention** Anakinra administered IV at 2.0mg/kg/hr for 72 hours continuously Concomitant treatments not reported **Comparison** Placebo administered IV at 2.0mg/kg/hr for 72 hours continuously Concomitant treatments not reported	**Critical Outcomes** • 28-day mortality **Important outcomes** • None reported
Sonmez et al 2018 Single centre, retrospective case series Hacettepe, Turkey	15 paediatric patients with a diagnosis of MAS (19 episodes) 4/19 episodes required PICU admission No subgroups reported	**Intervention** Anakinra (2mg/kg/day) within a median of 1 day after hospitalisation (increased to 4-6mg/kg/day in 2 patients) Treatment with anakinra was tapered 6 months after full clinical and laboratory remission Concomitant treatments included: • steroids • IVIG • ciclosporin A • plasmapheresis • etoposide **Comparison** None	**Critical Outcomes** • Adverse events (at median follow up 13 (range 6 to 24) months) **Important Outcomes** • Resolution time of fever after the introduction of anakinra • Time of discharge after anakinra initiation • Cessation time of steroid after anakinra initiation

Study	Population	Intervention and comparator	Outcomes reported
Wohlfarth et al 2019 Single centre, retrospective case series Vienna, Austria	8 adults admitted to ICU with multiple-organ dysfunction syndrome (MODS) linked to a diagnosis of HLH No subgroups reported	**Intervention** Anakinra (subcutaneous 100-200mg TDS) Median daily dose: 6mg/kg (range 4-8) Median duration treatment: 18 (7-42) days in survivors Concomitant treatments included: • steroids • IVIG • ganciclovir • antifungals • acyclovir **Comparison** none	**Critical Outcomes** • Survival to hospital discharge (timepoint not reported) • ICU duration of stay • Adverse events (timepoint not reported) **Important Outcomes** • Ferritin levels (baseline and day 14) • Length of hospital stay
Abbreviations: HLH - haemophagocytic lymphohistiocytosis, ICU - intensive care unit, IV - intravenous, IVIG - intravenous immunoglobulin, kg - kilogram, MAS - macrophage activation syndrome, mg - milligram, MODS - multiple-organ dysfunction syndrome, PICU - paediatric intensive care unit, RCT - randomised controlled trial, SC - subcutaneous, TDS - three times a day, USA - United States of America			
Footnotes: a. The outcomes listed in this table are listed in the way that they are described in each study. In some cases, the heading may differ from the exact outcomes listed in the PICO table. These outcomes have been included as they are best approximation to the specified critical or important outcome of interest. b. Included as predictive factors relate to subgroup outcomes. c. 763 patients (out of 906 originally recruited) completed the original RCT for anakinra for severe sepsis. This study is an analysis of the 43 patients who also had hepatobiliary dysfunction/ disseminated intravascular coagulation. d. The original RCT was a multicentre study and recruited 906 patients from 91 centres, 11 countries in Europe and North America. The distribution of the 43 patients included in the subgroup analysis was not reported.			

5. Results

In adults and children with 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 an RCT (Opal et al 1997) and four case series) provided evidence relating to in hospital and 30-day mortality. Mortality was

Outcome	Evidence statement
	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 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. 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 (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[3]. (**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%.**
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[4] days (range 3 to 118 days). For the 5/8 (63%) patients who were discharged from ICU, the

[3] 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 MOSF, the other 3/12 causes of death included fungal infection.
[4] 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
	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 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 (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 within 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). At 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

Outcome	Evidence statement
	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 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[5] (±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 IVIG **Certainty of evidence:** N/A	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. **No evidence was identified for this outcome.**

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

Outcome	Evidence statement
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 ciclosporine is relevant to patients because ciclosporine may be used (in combination with steroids with or without IVIG) to suppress the cell-mediated immune reactions. A reduction or cessation in ciclosporine 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-comparative results for people who were treated with anakinra for 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)**

Outcome	Evidence statement
	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. **Certainty of evidence:** N/A	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.**

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..

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 sJIA and 70% for 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.	

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

6. Discussion

This review considered the evidence for the clinical effectiveness and safety of anakinra compared to standard treatment in patients with HLH. The critical outcomes of interest were in hospital and 30-day mortality, ICU duration of stay, acquired infection and adverse events. Important outcomes were abolition of fever, hyperferritinaemia, length of hospital stay, complications and the use or change in dose of current treatments, specifically IVIG, steroids, etoposide and ciclosporin.

Evidence was available from one comparative cohort study and five case series with between eight and 44 patients with HLH who were treated with anakinra. Certainty in the comparative evidence for critical and important outcomes was very low when assessed using modified GRADE.

The comparative study by Shakoory et al (2019) was a retrospective analysis of a subgroup of adult patients originally recruited to participate in a large randomised controlled trial of either anakinra or placebo (both interventions were administered IV for 72 hours continuously) for

patients with severe sepsis (Opal et al 1997). Of the 763 patients with severe sepsis who completed the trial, 43 patients also had features of MAS (defined as the presence of both HBD and DIC). The focus of the subgroup analysis was to determine the efficacy of anakinra for 28-day survival by comparing the outcomes of the 43 patients with HBD/DIC with the rest of the patients with severe sepsis recruited to the original study (n=720). From this subgroup analysis, it was only possible to extract one outcome of relevance to this evidence review; 28-day mortality for the 43 patients with HBD/DIC treated with either anakinra or placebo. The analysis showed statistically significant lower mortality in patients treated with anakinra compared to placebo (34.6% vs 64.7%, p=0.0006) with a significantly lower risk of death (HR 0.28 (95%CI 0.11 to 0.71), p=0.0071. A 72% reduced risk of dying is a critically important outcome of value to patients although it should be noted that the confidence intervals around the hazard ratio are wide. In addition, the magnitude of the effect and its statistical significance should be interpreted with caution for a number of reasons. Analyses unplanned at the study outset and carried out after data acquisition are less reliable because the authors may have selected results for this analysis in the search for positive and reportable findings. The 43 patients were originally randomised to receive anakinra or placebo as part of an RCT which recruited 906 patients. However, the randomisation no longer applies to this subgroup and the study was not powered to detect a difference in outcome between anakinra and placebo for these patients. There was limited comparison of baseline characteristics for the anakinra and placebo treatment groups for the subgroup of patients. The authors did not describe any concomitant drugs that were given to patients in addition to either anakinra or placebo (and it is unlikely that none were given). We do not know if the concomitant treatments given pre-2000 would be considered relevant and contemporary adjuncts to anakinra or a comparator in the current NHS setting. The observed difference between the 28-day mortality for anakinra compared to placebo could be confounded by any between group differences in baseline characteristics or treatments.

The five case series (Eloseily et al 2019, Gregory et al 2019, Kumar et al 2017, Sonmez et al 2018, Wohlfarth et al 2019) each conducted a retrospective review of case notes in a single centre, spanning between two and ten years from 2007 to 2017. They reported descriptive, before and after results for a range of outcomes for patients who received anakinra. These case series provided no evidence for outcomes following treatment with anakinra compared to standard treatment in patients with HLH.

The case series available for inclusion in this review provide limited evidence for critical (in hospital mortality, ICU duration of stay, adverse events and acquired infection) and important (abolition of fever, hyperferritinaemia, length of stay, and the use of steroids) outcomes following treatment with anakinra for HLH. No evidence was available for usage of other drugs or complications associated with treatment with anakinra. Adverse events were not reported clearly in any of the studies. Due to the lack of good quality studies suitable for inclusion, we selectively extracted data from two case series which were not designed to evaluate the effect of anakinra for patients with HLH (16/33 patients and 13/19 patients were treated with anakinra in Gregory et al (2019) and Kumar et al (2017) respectively). As with the comparator cohort in the study by Shakoory et al 2019, the demographic and clinical characteristics specific to the 16 patients treated with anakinra were not reported in the case series by Gregory et al 2019.

In addition to the non-comparative nature of the case series study design, uncertainty about the results stemmed from a range of issues, all of which might have affected the outcomes.

- The non-uniform approach to anakinra treatment; two of the five case series (Eloseily et al 2019, Gregory et al 2019) did not report any information about when anakinra was initiated, the dose, or the duration of treatment. The remaining three case series reported different anakinra treatment regimens (100-200mg TDS for a median duration of 18 days (Wohlfarth et al 2019), 2mg/kg (no duration reported) (Sonmez et al 2018), and 100mg twice daily (no duration reported) (Kumar et al 2017). Concomitant treatments varied widely and in one case series (Gregory et al 2019), they were not reported (see Table 1).
- The patients included in the five case series appear to be heterogenous across demographic and clinical characteristics. Two case series reported outcomes for patients aged 18 years or over (Kumar et al 2017, Wohlfarth et al 2019); the remaining three case series reported outcomes for children and adolescents. Where reported, there was variation in the reported underlying cause of HLH across the case series.
- The diagnosis of HLH varied considerably across the five case series. This was necessary because of the retrospective approach to identifying patients for inclusion. The study authors relied on clinical consensus and/or a range of different diagnostic criteria; these included HLH-2004, HLH-2009, Henter's criteria, criteria for SLE-associated MAS, 2016 criteria for systemic JIA-associated MAS, the H-score for diagnosis of reactive haemophagocytic syndrome and the MAS/primary HLH score.
- It is not clear that all the patients included in the case series experienced the same severity of HLH. In some studies, admission to ICU was part of the inclusion criteria (Gregory et al 2019, Wohlfarth et al 2019) but it should be noted that only four out of 19 MAS episodes reported in the case series by Sonmez et al 2018 required admission to PICU. Only Gregory et al 2019 reported a baseline mortality risk. Variation in baseline HLH severity and mortality risk within and across the case series might have confounded the mortality and other outcomes.

Although mortality is unlikely to be affected by placebo effect in the Shakoory et al 2016 subgroup analysis, the internal validity of the results is very low due to the lack of clarity for a defined comparator group exposed to the same array of intervening variables. The heterogeneous nature of the diagnosis of HLH/MAS, the variation in clinical characteristics, underlying conditions, severity of HLH and wide range of concomitant treatments all contribute to the very low certainty associated with the reported outcomes from all the studies included in this review.

7. Conclusion

The key limitation to identifying the effectiveness of anakinra compared to standard treatment is the lack of reliable comparative studies, although it should be noted that HLH is a rare condition which presents in an acute/intensive care setting and therefore conducting large, prospective studies may be unrealistic. Very low certainty evidence from one retrospective comparative cohort study and five small, single centre retrospective case series reported outcomes for patients who were treated with anakinra for HLH in countries outside the UK. There was heterogeneity among the patients included in the studies (variation in diagnostic criteria, severity of disease and underlying disease), along with variation in anakinra and concomitant treatments. The outcomes reported may not be wholly attributable to anakinra. Apart from in hospital mortality, the number of studies reporting the other critical or important outcomes was low. The results from all these studies may not be generalisable to the current NHS in England.

The retrospective comparative cohort study provided very low certainty evidence that compared to placebo, anakinra reduced 28-day mortality in patients with HLH. The case series provided very low certainty evidence describing critical outcomes and important outcomes for patients with HLH who received anakinra. These studies provide no evidence about outcomes with anakinra compared to standard treatment in patients with HLH.

No studies reported results for the following important outcomes: complications, use or change in use of IVIG, etoposide or ciclosporin.

There is very low certainty evidence that patients with rheumatic/autoimmune diseases, particularly sJIA and that those treated with anakinra within five days of hospitalisation experienced a lower rate of mortality. Patients who received anakinra within five days of hospitalisation also had a greater drop in ferritin level compared to those who received anakinra after 5 days of hospitalisation. These results were based on one single centre, case series and should be interpreted with caution.

The very low certainty evidence from all these studies included in this review is insufficient to draw reliable conclusions about the clinical effectiveness and safety of anakinra compared to standard treatments in patients with HLH. No evidence on the cost effectiveness of anakinra compared to current standard treatments was identified.

Appendix A PICO Document

The review questions for this evidence review are:

1. In adults and children with HLH, what is the clinical effectiveness of anakinra compared with standard treatment?
2. In adults and children with HLH, what is the safety of anakinra compared with standard treatment?
3. In adults and children with HLH, what is the cost effectiveness of anakinra compared with standard treatment?
4. From the evidence selected, are there any subgroups of patients that may benefit from anakinra more than the wider population of interest?

PICO Table

P –Population and Indication	Adults and children (all ages) presenting with primary or secondary HLH[6] regardless of trigger condition requiring treatment for HLH as part of their clinical care. (Further subgroups that may be identified: • Patients with primary HLH • Patients with secondary HLH • Patients with sHLH trigger unknown • Patients with sHLH triggered by SJIA • Patients with sHLH triggered by AOSD • Patients with sHLH triggered by infection • Patients with sHLH triggered by a pre-existing rheumatology condition • Patients with sHLH triggered by malignancy • Patients with sHLH triggered by HSCT or CART cell therapy) [Information for searches][7]
I – Intervention	Anakinra (Kineret) 1-10 mg/kg, usually for 3-14 days by subcutaneous injection or intravenous infusion as first- or second-line treatment, alone or in combination with, corticosteroids or intravenous immunoglobulin (IVIG). [Studies in which ciclosporin and/or etoposide are given concurrently to anakinra should not be excluded].
C – Comparator(s)	Current standard treatment[8] with corticosteroids, intravenous immunoglobulin (IVIG), ciclosporin, methotrexate and/or etoposide without use of anakinra.

[6] diagnosis of HLH is based on either a, b or c.
a. criteria of HLH-2004 protocol for pHLH (five of eight or 1.fever, 2. splenomegaly, 3.cytopenias affecting at least two of three lineages in the peripheral blood, 4.hypertriglyceridemia and/or hypofibrinogenemia, 5.hemophagocytosis in bone marrow, spleen, or lymph Nodes, 6.low or absent NK-cell activity, 7.hyperferritinemia, and 8.high levels of sIL-2r. Patients with a molecular diagnosis consistent with HLH do not necessarily need to fulfil the diagnostic criteria)
b. H score/ferritin >10000/tissue diagnosis in sHLH
c. Advice of an MDT

[7] HLH may also referred to as MAS, MALSS, cytokine storm syndrome, cytokine release syndrome, hyperferritinaemia

[8] pHLH – HLH-2004 protocol (dexamethasone, IVIG, methotrexate, ciclosporin, etoposide). sHLH (extrapolated from HLH 2004), First line: High dose steroids (e.g. methylprednisolone 1g daily for 3-5 days) ,Second line: continued IV or oral corticosteroids, intravenous immunoglobulin (IVIG) (1g/kg for 2 days and repeated at 14 days

	[Studies in which ciclosporin and/or etoposide are given concurrently to IVIG should not be excluded].
O – Outcomes	<u>Critical to decision-making</u> 1. Efficacy (short and long-term outcomes) a. In hospital and 30-day mortality b. ICU duration of stay 2. Safety a. Acquired infection b. Adverse events <u>Important to decision-making</u> c. Abolition of fever d. Hyperferritinaemia – reduction in serum ferritin levels of 20-50% or more e. Length of hospital stay f. Complications –multiorgan failure, severe cognitive impairment, learning disabilities, nerve paresis, renal impairment and obstructive bronchiolitis etc. g. Use or change in dose of IVIG h. Use or change in dose of steroids i. Use or change in dose of etoposide j. Use or change in dose ciclosporin Cost effectiveness
Inclusion criteria	
Study design	Systematic review clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2010 - 2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines
Study design	Case reports, resource utilisation studies

if needed, or 0.5g/kg 4 weekly in children) plus consideration of ciclosporin (2-7 mg/kg/day), to reduce relapse or if MAS secondary to rheumatic disease but this is may be associated with significant neurotoxicity in the HLH context.

Appendix B Search strategy

Medline, Embase, Cochrane Library, TRIP database and NICE Evidence Search were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and case reports were excluded.

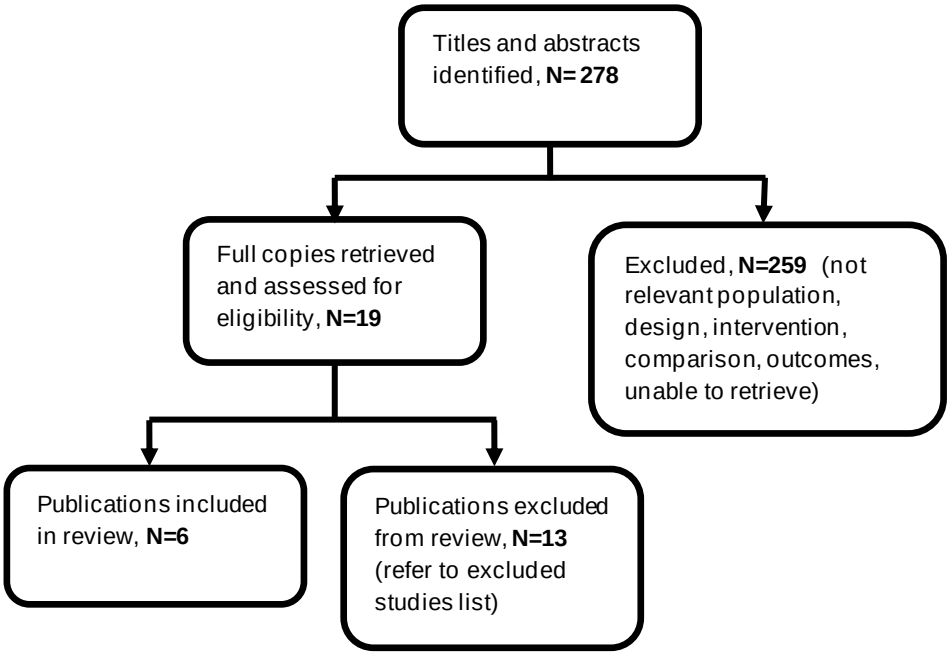
Search date: 30 January 2020.

Medline Search

# ▲	Searches
1	Lymphohistiocytosis, Hemophagocytic/
2	(H?emophagocytic lymphohistiocytosis or macrophage activation syndrome? or macrophage activation like syndrome? or cytokine storm syndrome or cytokine release syndrome or hyperferritin?emi*).ti,ab,kw.
3	(hlh or shlh or phlh).ti,ab,kw.
4	1 or 2 or 3
5	Interleukin 1 Receptor Antagonist Protein/
6	(anakinra or kineret or "interleukin 1 receptor antagonist protein" or "recombinant interleukin 1 receptor block*" or "recombinant interleukin 1 receptor antagonist*").ti,ab,kw
7	5 or 6
8	4 and 7
9	exp animals/ not humans/
10	8 not 9
11	limit 10 to (english language and yr="2010 -Current")

Appendix C Evidence selection

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
La Rosee P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019;133(23):2465-77.	Excluded. This paper reports recommendations for the management of HLH based on expert opinion. It does not report results of treatment with anakinra for patients with HLH
Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Critical care medicine. 2016;44(2):275-81.	Included in this review
Kumar B, Aleem S, Saleh H, Petts J, Ballas ZK. A Personalized Diagnostic and Treatment Approach for Macrophage Activation Syndrome and Secondary Hemophagocytic Lymphohistiocytosis in Adults. J Clin Immunol. 2017;37(7):638-43.	Included in this review

Appendix D Excluded studies table

Study reference	Reason for exclusion
Al-Mayouf SM, Fallatah R, Al-Twajery M, Alayed T, Alsonbul A. Outcome of children with systemic rheumatic diseases admitted to pediatric intensive care unit: An experience of a tertiary hospital. International Journal of Pediatrics and Adolescent Medicine. 2019;6(4):142-5.	2/41 PICU admissions were treated with anakinra. No results were reported for the treatment of HLH/MAS using anakinra.
Aytac S, Batu ED, Unal S, Bilginer Y, Cetin M, Tuncer M, et al. Macrophage activation syndrome in children with systemic juvenile idiopathic arthritis and systemic lupus erythematosus. Rheumatology International. 2016;36(10):1421-9.	No timepoint or additional information is available about the patients who died. It is not clear if they can be classed as 30-day mortality, in hospital mortality or post discharge from hospital mortality.
Barut K, Adrovic A, Sahin S, Tarcin G, Tahaoglu G, Koker O, et al. Prognosis, complications and treatment response in systemic juvenile idiopathic arthritis patients: A single-center experience. International Journal of Rheumatic Diseases. 2019;22(9):1661-9.	It is not clear what proportion of patients with MAS were treated with anakinra. No results were reported for the treatment of HLH/MAS using anakinra.
Barut K, Yucel G, Sinoplu AB, Sahin S, Adrovic A, Kasapcopur O. Evaluation of macrophage activation syndrome associated with systemic juvenile idiopathic arthritis: single center experience over a one-year period. Turk Pediatri Arsivi. 2015;50(4):206-10.	Only one outcome reported (mortality). We have already selected 1 comparator cohort study and 3 case series with a greater number of patients for this outcome.
Boom V, Anton J, Lahdenne P, Quartier P, Ravelli A, Wulffraat NM, et al. Evidence-based diagnosis and treatment of macrophage activation syndrome in systemic juvenile idiopathic arthritis. Pediatric Rheumatology Online Journal. 2015;13:55.	This review includes 1 study with results for anakinra (n=12 with MAS). This was published as a letter in 2011. There are no detailed results other than a narrative statement '…remission was reached in all patients…'
Kimura Y, Weiss JE, Haroldson KL, Lee T, Punaro M, Oliveira S, et al. Pulmonary hypertension and other potentially fatal pulmonary complications in systemic juvenile idiopathic arthritis. Arthritis care & research. 2013;65(5):745-52.	Study describing disease course and treatment. No results reported for the treatment of HLH/MAS using anakinra.
Lenert A, Yao Q. Macrophage activation syndrome complicating adult onset Still's disease: A single center case	Only one outcome reported (mortality). We have

series and comparison with literature. Seminars in Arthritis & Rheumatism. 2016;45(6):711-6.	already selected 1 comparator cohort study and 3 case series with a greater number of patients for this outcome.
Neel A, Wahbi A, Tessoulin B, Boileau J, Carpentier D, Decaux O, et al. Diagnostic and management of life-threatening Adult-Onset Still Disease: A French nationwide multicenter study and systematic literature review. Critical Care. 2018;22(1).	Cannot confirm that all the patients treated with anakinra had HLH/MAS
Rajasekaran S, Kruse K, Kovey K, Davis AT, Hassan NE, Ndika AN, et al. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children. Pediatric Critical Care Medicine. 2014;15(5):401-8.	Larger case series (n=44) selected which reports the same outcomes as this case series (n=8).
Rigante D, Emmi G, Fastiggi M, Silvestri E, Cantarini L. Macrophage activation syndrome in the course of monogenic autoinflammatory disorders. Clinical Rheumatology. 2015;34(8):1333-9.	Discussion paper/ descriptive review. No results reported for the treatment of MAS using anakinra.
Ruscitti P, Cipriani P, Liakouli V, Iacono D, Pantano I, Caso F, et al. Prescribing motivations and patients' characteristics related to the use of biologic drugs in adult-onset Still's disease: analysis of a multicentre "real-life" cohort. Rheumatology International. 2020;40(1):107-13.	Mixed population. Cannot determine outcomes that only relate to the treatment of HLH/MAS using anakinra.
Thueringer JT, Doll NK, Gertner E. Anakinra for the treatment of acute severe gout in critically ill patients. Seminars in Arthritis & Rheumatism. 2015;45(1):81-5.	No results reported for the treatment of HLH/MAS using anakinra.
Zhou S, Qiao J, Bai J, Wu Y, Fang H. Biological therapy of traditional therapy-resistant adult-onset still's disease: An evidence-based review. Therapeutics and Clinical Risk Management. 2018;14:167-71.	Descriptive review - No results reported for the treatment of HLH/MAS using anakinra.

Appendix E Evidence Table

Study details	Population	Interventions	Study outcomes	Appraisal and Funding

Eloseily EM, Weiser P, Crayne CB, Haines H, Mannion ML, Stoll ML, Beukelman T, Prescott Atkinson T, Cron RQ. Benefit of Anakinra in Treating Pediatric Secondary Hemophagocytic Lymphohistiocytosis. Arthritis & Rheumatology. 2019;12:12.
 	
Study location
Alabama, USA
 	
Study type
Single centre, retrospective case series
 	
Study aim
'to assess the benefit of anakinra in treating paediatric patients with sHLH/MAS associated with rheumatic/nonrheumatic conditions'
 	
Study dates
January 2008-December 2016
	Inclusion criteria
	Consecutive paediatric patients with secondary HLH/MAS treated with anakinra
	
	Exclusion criteria
	Patients less than 1 year of age were excluded (to exclude patients with primary HLH)
	
	Sample size
	n=44
	
	Baseline characteristics
	Age (mean ± SD): 10.3±5.7 years
	Male: 19/44 (43%)
	42/44 (95%) were classified as sJIA associated MAS
	
	Secondary HLH or MAS was confirmed using at least 1 of 6 different sets of criteria:
	• HLH-2004 criteria (n=9)
	• HLH-2009 criteria (n=17)
	• criteria for SLE-associated MAS (n=18), the 2016 criteria for sJIA–associated MAS (n=19)
		Intervention details (n=44)
		Anakinra
		(dose, timing of initiation after diagnosis and duration of treatment not reported)
		
		Concomitant therapies included:
		• glucocorticoids (73%)
		• ciclosporin A (25%)
		• IVIG (9%)
		• etoposide (9%)
		• tocilizumab (5%)
		• abatacept, rituximab, cyclophosphamide, plasmapheresis in 1 patient each
		
		Comparator details
		none
			Critical outcomes
			
			In hospital mortality
			Overall mortality (timepoint not reported) 12/44 (27%)
			The cause of death was septic shock and/or multiorgan system failure in 9/12 patients
			
			Acquired infection
			6/12 patients who died had systemic infections (5 had positive fungal cultures) although the authors state that *'There was no association with the timing of anakinra administration and infection.'*
			
			Important outcomes
			
			Abolition of fever
			Defervescence after anakinra start (mean±SD days):
			• Total: 1.7±1.1 (n=44)
			  ○ survivors: 1.6±1
			  ○ non-survivors: 2±1.4
			
			Ferritin level
			• Pre-treatment vs <u>within</u> 15 days anakinra (mean±SD ng/mL): 33,316 ± 56,514 vs 14,435 ± 79,842 (reported to be a 57% decrease)
			• Change <u>at 15 days</u> (mean ± SD ng/ml): 19,256 ± 66,334
			• Decrease at 15 days (mean ± SD %): 72 ± 62
				This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case Series.
				1. Yes
				2. Yes
				3. Yes
				4. Yes
				5. Yes
				6. Yes
				7. Yes
				8. Unclear
				9. Yes
				10. Yes
				
				Other comments:
				This was a retrospective case series with no comparator treatment.
				All patients were treated with anakinra although when treatment started, the dose and duration of treatment is unknown.
				Concomitant treatments varied considerably and the number of concomitant treatments administered to patients was not reported. It is not clear to what extent outcomes can be attributed to anakinra alone.
				The mean follow up for all the patients included in the study and the timepoints for outcomes are not reported. Although not specified, it is reasonable to assume that death due to septic shock or multiorgan system failure would have occurred in hospital. Adverse

Study details	Population	Interventions	Study outcomes	Appraisal and Funding

	•HScore for diagnosis of reactive hemophagocytic syndrome (n=20)
	• MAS/primary HLH score (n=21)
	
	Underlying diseases
	• sJIA (n=13)
	• Malignancy(leukaemia) (n=3)
	• Lupus and related conditions (n=10)
	• Infection alone (n=6)
	• Other/unknown (n=12)
	
	16/44 (36%) patients had no identifiable rheumatic disease
	13/34 (38%) had infection along with underlying disorders
			Length of hospital stay
			Hospitalisation (mean±SD days):
			• Total: 30±40 (n=44)
			  ○ Survivors: 18±16
			  ○ Non-survivors: 62±62
			
			Other
			Predictive factors correlated with outcomes:
			• Increased mortality rate
			  ○ Thrombocytopaenia: p=0.025
			  ○ Hscore cell lineage: p=0.033
			  ○ STXBP2 mutation: p=0.004
			• Decreased mortality rate
			  ○ Earlier start to anakinra[9]: p=0.046
			  ○ Systemic JIA: p=0.006
			• Improvement in ferritin level
			  ○ Earlier start to anakinra treatment: p=0.001
			
			Survival rate by diagnosis (timepoint not reported)
			• Rheumatic/autoimmune diseases 20/23 (86%) including
			  ○ sJIA 13/13 (100%)
			  ○ SLE & related conditions: 7/10 (70%)
			• Infection alone: 3/6 (50%)
			• Malignancy (leukaemia): 0/3 (0%)
			• Other/unknown: 9/12 (75%)
				events/unanticipated events related to treatment with anakinra were not clearly reported.
				
				Source of funding: No funding declaration published

Gregory J, Greenberg J, Basu S. Outcomes	**Inclusion criteria** Paediatric patients with	**Intervention details (n=16):** Anakinra	**Critical outcomes**	This study was appraised using the Joanna Briggs Institute 2017

[9] Within ≤5 days of hospitalisation

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Analysis of Children Diagnosed With Hemophagocytic Lymphohistiocytosis in the PICU. Pediatric Critical Care Medicine. 2019;20(4):e185-e90 **Study location** Washington DC, USA **Study type** Single centre, retrospective case series **Study aim** 'to identify clinical features that may be associated with worse outcomes including mortality, hospital and ICU length of stay and functional and cognitive impairments on discharge' **Study dates** 2007-2017	HLH (ICD9 or ICD 10 codes for HLH). There were 42 PICU admissions, only the first ICU admission was included in the case series **Exclusion criteria** not stated **Sample size** n=16 The study included 33 patients. Relevent outcomes for the 16 patients who received anakinra was extracted for inclusion in this review. **Baseline characteristics** (n=33): Median age: 98 months (IQR 27-186) Female: 19 (57%) Paediatric risk of Mortality III score (median IQR): 9 (7-16) Type of HLH Primary HLH: 7/33 (21%) Secondary HLH: 22/33 (67%) Unknown HLH type: 4/33 (12%) Steroid treatment: 31/33 (94%)	(dose, duration of treatment and concomitant drugs administered with anakinra not reported) **Comparator:** None	**In hospital mortality** (timepoint not reported) 5/16 (31%) patients treated with anakinra did not survive to hospital discharge	Critical Appraisal Checklist for Case Series. The appraisal was conducted in relation to the patients within this study who received anakinra. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. No 7. No 8. No 9. Yes 10.Yes **Other comments:** This was a retrospective case series of 33 patients with HLH but only 48% were treated with anakinra. Baseline characteristics for this subgroup are unknown. The details of both anakinra treatment (when initiated, dose, duration of treatment) and concomitant treatments are unknown. The mean follow up for the patients treated with anakinra and the timepoint for mortality was not reported. The median paediatric mortality risk was reported for the wider population, and not for those treated with anakinra. We noted that the IQR ranged from 7 to 16; it is not clear to what extent the unreported initial mortality risk score of patients who were treated with anakinra could have biased the outcome. Adverse events related to treatment with anakinra were not clearly reported.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
				Source of funding: No study funding declared *'The authors have not disclosed any potential conflicts of interest'.*
Kumar B, Aleem S, Saleh H, Petts J, Ballas ZK. A Personalized Diagnostic and Treatment Approach for Macrophage Activation Syndrome and Secondary Hemophagocytic Lymphohistiocytosis in Adults. Journal of Clinical Immunology. 2017;37(7):638-43 **Study location** Iowa, USA **Study type** Single centre, retrospective case series **Study aim** 'to assess the clinical features and outcomes based on therapeutic options adopted during hospital stay for adult patients with MAS and sHLH' **Study dates**	**Inclusion criteria** Adults ≥18 years with MAS/sHLH (who met 5/8 Henter's criteria, or at least 4/6 criteria that were tested). **Exclusion criteria** not stated **Sample size** n=13 The study included 19 patients. Data for the 13 patients who received anakinra was extracted for inclusion in this review **Baseline characteristics** (n=19): Median age: 48 years Male: 6/19 (32%) Underlying disease [n (%)] Adult-onset Still's disease: 5 (26.3) Other autoimmune diseases[10]: 9 (47.4) Lymphoproliferative disorders: 3 (15.8)	**Intervention details (n=13):** Anakinra 100mg subcutaneously twice daily (duration of treatment was not reported) Concomitant treatments were: • steroid+ciclosporin A+IVIG (n=10) • steroid+IVIG+ tocilizumab (n=1) • steroid+ciclosporin A+IVIG+tocilizumab (n=1) • none (n=1) **Comparator:** None	**Critical outcomes** **In hospital mortality** (timepoint not reported) 4/13 (31%) patients treated with anakinra did not survive to hospital discharge 3 of these patients had underlying leukaemia/lymphoma and had received anakinra as part of palliative care treatment	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case Series. The appraisal was conducted in relation to the patients within this study who received anakinra. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. No 7. Yes 8. No 9. Yes 10. Not applicable **Other comments:** This was a retrospective study of 19 patients with HLH but only 68% were treated with anakinra. Baseline characteristics for this subgroup are unknown. The mean follow up for the patients treated with anakinra and the timepoint for mortality was not reported. Although all patients received the same anakinra dose regimen, when treatment was initiated or the duration of treatment is unknown. In

[10] Includes anti-neutrophil cytoplasmic autoantibody-associated vasculitis, cryoglobulinemic vasculitis, autoimmune hepatitis, celiac disease, Hashimoto's thyroiditis, rheumatoid arthritis, systemic lupus erythematosus, and ulcerative colitis

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
January 2010 to October 2015	Unknown: 2 (10.5) Prior immunosuppressive therapy: 9/19 (47.4%)			addition, there was significant variation in concomitant treatments. These variations, along with the underlying diseases and the administration of anakinra as part of palliative care treatment may have resulted in a higher overall mortality rate. Adverse events related to treatment with anakinra were not reported **Source of funding**: No study funding declared *'The authors have no relevant financial disclosues.'* *'The authors declare that they have no conflicts of interest.'*
Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Critical Care Medicine. 2016;44(2):275-81 **Study location** The location of the 43 patients in this subgroup is not reported. The original RCT was a multicentre	**Inclusion criteria** Adults (43 of 763 patients who had completed the original RCT for anakinra for severe sepsis trial) with sepsis with multi-organ dysfunction and /or shock with features of MAS (defined as the presence of hepatobiliary dysfunction/ disseminated intravascular coagulation) **Exclusion criteria** not stated **Sample size** n=43	**Intervention details (n=26):** Anakinra administered IV at 2.0 mg/kg/hr for 72 hours continuously Concomitant treatments not reported **Comparator details (n=17):** Placebo administered IV at 2.0 mg/kg/hr for 72 hours continuously Concomitant treatments not reported	**Critical outcomes** **30-day mortality** **28-day mortality** anakinra vs. placebo: 34.6% v. 64.7%, p=0.0006 HR death 0.28 (0.11-0.71), p=0.0071	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for (comparative) cohort studies. The appraisal was conducted in relation to this subgroup analysis of patients diagnosed with MAS. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Not applicable 11. Yes **Other comments:**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
study (91 centres from 11 countries in Europe and North America) **Study type** Comparator cohort study (re-analysis of sepsis with MAS subgroup dataset from a prior phase III randomized interleukin-1 receptor antagonist trial in severe sepsis (Opal et. Al 1997) **Study aim** 'to determine the efficacy of anakinra compared to placebo in improving 28-day survival in sepsis patients with features of MAS' **Study dates** Initiated 1993 – final recruitment date not specified in original RCT publication (Opal et al 1997)	**Baseline characteristics** (n=43): Treatment with anakinra (n=26, 60.5%) Age (mean±SD): 49.6±12.7 years Female: 12 (46.2%) Acute kidney injury 17 (65.4%) Acute respiratory distress syndrome 6 (23.1%) Risk of death: 0.57±0.22 Treatment with placebo (n=17, 39.5%) Age(mean±SD): 56.3±19.4 years Female: 8 (47.1%) Acute kidney injury: 9(52.9%) Acute respiratory distress syndrome: 3 (17.7%) Risk of death: 0.53±0.25 No between group differences for age (p=0.18), sex (p=0.95), acute kidney injury (p=0.41), acute respiratory distress syndrome (p=0.28), risk of death (p=0.54)			This was a nonrandomised retrospective subgroup analysis of an RCT investigating a wider group of sepsis patients. The study was not powered to detect a difference in outcome between the anakinra/placebo treatment groups for this small subgroup (43 out of 763 patients who completed the original RCT. There were no between group differences for the baseline characteristics reported. The treatments were defined clearly and the outcome (mortality) is not subject to bias. It should be noted that this was a study of patients recruited to a trial of anakinra for sepsis which was published in 1997. Concomitant drugs were not reported for either arm of this analysis. We do not know if the comparator treatment arm or concomitant drugs (if they were given) are relevant to current treatment options, and if the difference in 28-day mortality is generalisable to the NHS in 2020. **Source of funding:** No study funding declared Although 5/8 authors declared potential conflicts of interest, it is not clear to what extent the declared sources directly funded or influenced this subgroup analysis
Sonmez HE, Demir S, Bilginer Y, Ozen S. Anakinra treatment in	**Inclusion criteria** Paediatric patients with MAS secondary to sJIA	**Intervention details (n=15):**	Median time of follow-up:13 (6 to 24) months	This study was appraised using the Joanna Briggs Institute 2017

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
macrophage activation syndrome: a single center experience and systemic review of literature. Clinical Rheumatology. 2018;37(12):3329-35 **Study location** Hacettepe, Turkey **Study type** Single centre, retrospective case series **Study aim** 'to report the experiences of treating pediatric MAS patients with anakinra' **Study dates** January 2015-January 2017	or AIDS and treated with anakinra All patients fulfilled Ravelli's criteria 13/19 episodes (68.4%) met the HLH-2004 criteria **Exclusion criteria** not stated **Sample size** n=15 (19 episodes included in the analysis) including sJIA, n=13 AIDS, n=2 PICU admission: 4/19 (21%) episodes **Baseline characteristics** Median age: 7 (range 0.5 to 16) years Female: 9/15 (60%) Ferritin(ng/mL): 7665 (range 760-95,400)	Anakinra (2mg/kg/day) within a median of 1 day after hospitalisation (increased to 4-6mg/kg/day in 2 patients) Treatment with anakinra continued throughout hospital admission Concomitant treatments for 19 episodes of MAS were: • steroid±IVIG (7 episodes) • steroid+ciclosporin A±IVIG (6 episodes) • steroid+ciclosporin A±IVIG +plasmapheresis (3 episodes) • steroid+ciclosporin A±IVIG +plasmapheresis +etoposide (3 episodes) **Comparator:** None	**Critical to decision-making** **Adverse Events** *'none of the patients experienced severe injection site reactions' and 'one patient developed vitiligo and treatment was switched to canakinumab'* (timepoint not reported). **Important to decision-making** **Abolition of fever** Median resolution time of the fever after the introduction of anakinra: 2 (1 to 4) days **Length of hospital stay** Median time of discharge after anakinra initiation: 12 (8 to 21) days **Use or change in dose of steroids** Median cessation time of steroid after anakinra initiation: 10 (4 to 13) weeks	Critical Appraisal Checklist for Case Series 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:** This was a retrospective study of 15 patients who had 19 MAS episodes, 13 of which met 2004-HLH criteria. The median follow-up time was 13 months and therefore outcomes which occurred post-hospital discharge were reported (change in steroid use). As well as anakinra, all patients were treated with steroids and IVIG. The anakinra treatment dose varied and there was variation in concomitant treatments with some episodes being treated with up to 3 additional treatments. Adverse events were reported in the narrative only. It is not clear to what extent the outcomes and adverse events were attributable to anakinra or concomitant treatments. **Source of funding**: No study funding declared
Wohlfarth P, Agis H, Gualdoni GA, Weber J,	**Inclusion criteria**	**Intervention details (n=8):** Anakinra	**Critical to decision-making**	This study was appraised using the Joanna Briggs Institute 2017

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Staudinger T, Schellongowski P, et al. Interleukin 1 Receptor Antagonist Anakinra, Intravenous Immunoglobulin, and Corticosteroids in the Management of Critically Ill Adult Patients With Hemophagocytic Lymphohistiocytosis. Journal of Intensive Care Medicine. 2019;34(9):723-31 **Study location** Vienna, Austria **Study type** Single centre, retrospective case series **Study aim** 'to report on the outcome of using anakinra (interleukin 1 receptor antagonist) in combination with IVIG and/or CS to treat critically ill adult patients with reactive HLH' **Study dates** March 2014 to March 2016	Adults≥18 years admitted to ICU with multiple-organ dysfunction syndrome (MODS) linked to a diagnosis of HLH. HLH was based on clinical consensus and included patients with less than 5 fulfilled HLH-2004 criteria **Exclusion criteria** not stated **Sample size** n=8 **Baseline characteristics** Mean Age: 38 (range 20 to 58) years Males: 4 (50%) Suspected reactive HLH: median H-score 214 range 171-288 (94% (55-99%) probability of the diagnosis) SOFA score at HLH diagnosis: 9.5, range 6-14 Vasopressors and invasive mechanical ventilation: 7/8 (88%) Ferritin (median µg/L): 32,419 (946-79,586)	• Administered subcutaneously 100-200mg TDS • Median daily dose: 6 (range 4-8) mg/kg • Median duration anakinra treatment: 18 (7-42) days in survivors In addition to anakinra, concomitant treatments were: • steroid (n=1) • steroid+ IVIG (n=4) • steroid+IVIG+gancylcovir+ antifungals (n=1) • IVIG+acyclovir or ganciclovir (n=2) Anakinra and steroid treatment was tapered according to clinical improvement, resolution of organ dysfunction, decline in inflammatory markers **Comparator:** None	**In hospital mortality** 4/8 (50%) survived to hospital discharge (no timepoint reported) **ICU duration of stay (mean)** • All patients (n=8): 36* (range 3 to 118) days • Survivors (n=5): 43.6 (range 6 to 118) days *The published narrative states 15 not 36 days but this is not consistent with the results in table 2 of the published study. The ICU duration of stay days are extracted by the reviewer from data reported in table 2 of the publication **Important to decision-making** **Hyperferritinaemia – reduction in serum ferritin levels of 20-50% or more** Ferritin levels baseline vs day 14 (median µg/L): 32,419 (946-79,586) (n=8) vs 2,754 (489-9036) (n=7). No statistical analysis was reported due to missing data/lack of power **Length of hospital stay (mean)*:** • All patients (n=8): 65.75 (range 5 to 190) days • Survivors (n=4): 99.25 (range 32 to 190) days *Reviewer calculations extracted from table 2 of publication **Adverse events – '***no unscheduled treatment discontinuations or adverse events considered attributable to the*	Critical Appraisal Checklist for Case Series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:** This was a small retrospective study of 8 adults. The results are descriptive only. There was a non-uniform approach to anakinra treatment dose and duration of treatment. The number and type of concomitant treatments varied. The very wide ranges reported for length of stay in ICU and in hospital should be noted. Adverse events were reported in the narrative only. It is not clear to what extent the outcomes and adverse events were attributable to anakinra or concomitant treatments. **Source of funding:** No study funding declared and authors declared *"no potential conflict of interest with respect to the research, authorship and/or publication of this article."*

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			administration of anakinra were documented.' *'No overt treatment toxicity reported'*	

Abbreviations:
AIDS – acquired immunodeficiency syndrome, CI – confidence interval, HLH - haemophagocytic lymphohistiocytosis, HR – hazard ratio, hr – hour, H-Score – haemophagocytic diagnostic syndrome score, ICU – intensive care unit, IQR – interquartile range, IVIG – intravenous immunoglobulin, kg - kilogram, LOS – length of stay, MAS - macrophage activation syndrome, mg – milligram, µg/L – micrograms per litre, ng/mL – nanograms per millilitre, PICU – paediatric intensive care unit, SD – standard deviation, sHLH - secondary haemophagocytic lymphohistiocytosis, sJIA - systemic juvenile idiopathic arthritis, SLE - systemic lupus erythematosus, SOFA – sequential organ failure assessment, TDS – three times daily, USA – United States of America

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE Profiles

Table 1: In adults and children with HLH, what is the clinical effectiveness and safety of anakinra compared with standard treatment?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Treatment with anakinra	Treatment with placebo	Result		
In hospital and 30-day mortality (1 comparative cohort study, 4 case series)									
28-day mortality (number and proportion alive)									
1 comparative cohort study Shakhoory et al 2016	Serious limitations[1]	No serious indirectness	Not applicable	No serious imprecision	n=26	n=17	Anakinra vs placebo: 36.4% vs 64.9%, p=0.0006 HR death: 0.28 (95% CI 0.11-0.71), p=0.0071	Critical	Very Low
Survival to hospital discharge[2] (timepoint not reported)									
1 case series Eloseily et al 2019	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	n=44	None	12/44 (27%) patients treated with anakinra did not survive to hospital discharge	Critical	Very Low
1 case series Gregory et al 2019	Very serious limitations[5]	Serious indirectness[4]	Not applicable	Not calculable	n=16	None	5/16 (31%) patients treated with anakinra did not survive to hospital discharge	Critical	Very Low
1 case series Kumar et al 2017	Very serious limitations[6]	Serious indirectness[4]	Not applicable	Not calculable	n=13	None	4/13 (31%) patients treated with anakinra did not survive to hospital discharge	Critical	Very Low
1 case series Wohlfarth et al 2019	Very serious limitations[7]	Serious indirectness[4]	Not applicable	Not calculable	n=8	None	4/8 (50%) patients treated with anakinra did not survive to hospital discharge	Critical	Very Low

ICU duration of stay									
ICU length of stay (mean, days)[8]									
1 case series Wohlfarth et al 2019	Very serious limitations[7]	Serious indirectness[4]	Not applicable	Not calculable	n=8	None	All patients (n=8): 36[a] (range 3 to 118) days Patients discharged from ICU (n=5): 43.6 (range 6 to 118) days	Critical	Very Low
Acquired infection									
Systemic infection (timepoint not reported)									
1 case series Eloseily et al 2019	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	n=44	None	6/12 patients who died had systemic infections (5 had positive fungal cultures) although the authors stated that *'There was no association with the timing of anakinra administration and infection.'*	Critical	Very Low
Adverse events									
Adverse events (timepoint not reported)									
1 case series Sonmez et al 2018	No serious limitations	Serious indirectness[4]	Not applicable	Not calculable	n=15	None	*'none of the patients experienced severe injection site reactions' and* *'one patient developed vitiligo and treatment was switched to canakinumab'.*	Critical	Very Low
1 case series Wohlfarth et al 2019	Very serious limitations[7]	Serious indirectness[4]	Not applicable	Not calculable	n=8	None	*'no unscheduled treatment discontinuations or adverse events considered attributable to the administration of anakinra were documented.'* *'No overt treatment toxicity reported'*	Critical	Very Low
Abolition of fever									
Defervescence after anakinra start (mean±SD days):									

1 case series Eloseily et al 2019	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	n=44	None	Total: 1.7±1.1 days • Survived: 1.6±1 • Died: 2±1.4	Important	Very Low
Resolution time of the fever after the introduction of anakinra (median days)									
1 case series Sonmez et al 2018	No serious limitations	Serious indirectness[4]	Not applicable	Not calculable	n=15	None	2 (range 1–4) days	Important	Very Low
Hyperferritinaemia – reduction in serum ferritin levels of 20-50% or more									
Mean Ferritin level 15 days after treatment initiation with anakinra (mean±SD ng/ml):									
1 case series Eloseily et al 2019	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	n=44	None	Pre-treatment vs within 15 days anakinra (mean±SD ng/ml): 33,316 ± 56,514 vs 14,435 ± 79,842 i.e. 57% decrease Change at 15 days (mean ± SD ng/ml): 19,256 ± 66,334 Decrease at 15 days (mean ±SD %): 72 ± 62	Important	Very Low
Median Ferritin level 14 days after treatment initiation with anakinra (median µg/L)									
1 case series Wohlfarth et al 2019	Very serious limitations[7]	Serious indirectness[4]	Not applicable	Not calculable	n=8	none	Ferritin levels baseline vs day 14 (median µg/L): 32,419 (946 to 79,586) (n=8) vs 2,754 (489 to 9036) (n=7)	Important	Very Low
Length of hospital stay									
Hospitalisation (mean±SD days)									
1 case series Eloseily et al 2019	Serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	n=44	None	Total: 30±40 days [Survived (n=32) vs died (n=12): 18±16 vs 62±62, p=0.0005]	Important	Very Low

Time of discharge after anakinra initiation (median days)									
1 case series Sonmez et al 2018	No serious limitations	Serious indirectness[4]	Not applicable	Not calculable	n=15	None	12 days (range 8 to 21)	Important	Very Low
Length of hospital stay (mean days)									
1 case series Wohlfarth et al 2019	Very serious limitations[7]	Serious indirectness[4]	Not applicable	Not calculable	n=8	none	Total: 65.75 days (range 5 to 190) 99.25 days (32 to 190) for 4 survivors to hospital discharge	Important	Very Low
Use or change in dose of steroids									
Cessation time of steroid after anakinra initiation (weeks)									
1 case series Sonmez et al 2018	No serious limitations	Serious indirectness[4]	Not applicable	Not calculable	n=15	None	10 weeks (range 4–13)	Important	Very Low

Abbreviations:

CI – confidence interval, HR – hazard ratio, ICU – intensive care unit, LOS – length of stay, ng/mL – nanograms per millilitre, SD – standard deviation, µg/L – micrograms per litre

Footnotes:

1 Unclear whether confounding factors were identified and concomitant drugs were not specified
2 Included as a proxy for in-hospital mortality
3 Unclear reporting of results
4 No comparison across treatment arms available and variation in concomitant treatments administered with anakinra
5 Reporting of the participants' demographics and clinical information and outcomes was not clear
6 Reporting of the participants' demographics and outcomes was not clear
7 It was unclear if the study had consecutive or complete inclusion of participants
8 The mean ICU LOS are based on reviewer calculations taken from absolute data reported in the author's table 2

a The narrative in the publication states 15 not 36 days but this is not consistent with the detailed results in the author's table 2

Glossary (adapted from the NICE Glossary)

Adverse event Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.

Case series Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.

Comparative cohort study An observational study with two or more groups (cohorts) of people with similar characteristics. One group has a treatment, is exposed to a risk factor or has a particular symptom and the other group does not.

Confidence interval (CI) A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).

Hazard Ratio (HR) The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.

P-value (p) The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.

Randomised controlled trial (RCT) A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.

Standard deviation (SD) A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.

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