

COVID 19 rapid evidence summary: Anakinra for COVID-19 associated secondary haemophagocytic lymphohistiocytosis

Evidence summary

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Key messages

The content of this evidence review was up-to-date on 13 May 2020. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Haemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome, which can lead to a cytokine storm, tissue damage and multi-organ failure. It has a high mortality rate. Primary HLH is an inherited condition, which presents mainly in childhood and may be associated with immunodeficiency. Secondary HLH (sHLH) usually occurs in previously immunocompetent people and may be triggered by autoimmune or autoinflammatory disease (when it is called macrophage activation syndrome [MAS]), malignancy (especially haematological malignancy) or, most often, infection (when it may be indistinguishable from sepsis). Viral infections are the most common cause of secondary sHLH ([Carter et al. 2019](#)).

The COVID-19 virus (SARS-CoV-2) can produce a profound cytokine response in the host, with raised levels of many inflammatory mediators. Observational studies have shown an association between systemic inflammation, severity and adverse outcomes in COVID-19 ([Huang et al. 2020](#), [Ruan et al. 2020](#), [Zhou et al. 2020](#)). A hyperinflammatory response develops in some people with COVID-19, which may be localised to the lungs or lead to widespread systemic illness and sHLH ([McGonagle et al. 2020](#)).

Treatment of sHLH is with immunosuppressive therapy (including corticosteroids, intravenous immunoglobulin [IVIG], anakinra and etoposide) combined with treatment of the triggering illness ([Carter et al. 2019](#)). There remains uncertainty about whether corticosteroids are beneficial to people with severe forms of COVID-19 acute respiratory distress syndrome (ARDS) or not ([Villar et al. 2020](#) and [Wu et al. 2020](#)). Both corticosteroids and etoposide may also increase the risk of secondary infection in COVID-19. IVIG is scarce and expensive and supplies are being requisitioned to ensure patients on chronic replacement have their treatment protected. There is currently no validated treatment for the SARS-CoV-2 virus.

Anakinra is a recombinant interleukin-1 (IL-1) receptor antagonist that blocks the biologic activity of natural IL-1 by competitively inhibiting the binding of IL-1 to the interleukin-1 type receptor ([Kineret summary of product characteristics](#)). IL-1 is a proinflammatory mediator produced in response to infection and is central to the hyperinflammation seen in cytokine storm syndromes such as sHLH ([Mehta et al 2020](#)).

Anakinra is licensed as a subcutaneous injection for treating adults with rheumatoid arthritis, and people aged at least 8 months with Still's disease or cryopyrin-associated periodic syndromes ([Kineret summary of product characteristics](#)). It is not licensed for sHLH or for intravenous administration.

Anakinra has been used to treat a range of cytokine storm syndromes and appears to be well tolerated ([Mehta et al 2020](#)). It was associated with reduced mortality in patients with sepsis and features of MAS (a type of sHLH) in a post-hoc analysis (n=43) of a phase 3 trial ([Shakoory et al 2016](#)).

Anakinra is recommended (off label) in treatment algorithms for sHLH ([Carter et al. 2019](#) and [La Rosee et al. 2019](#)) as part of a multi-disciplinary team decision-making process. In critical illness, subcutaneous absorption can be unreliable and intravenous dosing is sometimes used in clinical practice to achieve a higher and faster maximal plasma concentration ([Mehta et al 2020](#)).

This evidence review considers the clinical effectiveness, safety and cost effectiveness of anakinra

for treating sHLH triggered by SARS-CoV-2 in people of all ages. The research questions are:

1. In adults and children with sHLH triggered by SARS-CoV-2 or a similar coronavirus, what is the clinical effectiveness of anakinra compared with supportive treatment?

Supportive care may involve treatment with corticosteroids, IVIG, etoposide, organ support (ventilation, renal replacement therapy, transfusions etc) and antimicrobials.

2. In adults and children with sHLH triggered by SARS-CoV-2 or a similar coronavirus, what is the safety of anakinra compared with supportive treatment?
3. In adults and children with sHLH triggered by SARS-CoV-2 or a similar coronavirus, what is the cost effectiveness of anakinra compared with supportive treatment?
4. From the evidence selected, are there any subgroups of patients that may benefit from anakinra more than the wider population of interest?

No relevant papers were identified in the searches undertaken for this evidence review. Therefore, no evidence is available to determine whether anakinra is effective, safe or cost effective for treating adults and children with sHLH triggered by SARS-CoV-2 or a similar coronavirus.

Some new studies have considered intravenous anakinra for related conditions including hyperinflammation in people with COVID-19 and ARDS. However, administering anakinra intravenously is off label, which raises safety concerns. Also, these studies do not compare anakinra with other treatments such as tocilizumab.

At this time, policy decisions on whether anakinra should be used for treating COVID-19 associated sHLH will need to consider data extrapolated from studies assessing anakinra for related conditions, such as MAS, non-coronavirus sHLH and hyperinflammation in people with COVID-19 and ARDS.

Factors for decision making

Effectiveness and safety

No studies were found considering the effectiveness, safety or cost effectiveness of anakinra in adults and children with sHLH triggered by SARS-CoV-2 or a similar coronavirus.

Discussion and limitations of the evidence

No published evidence was found to support using anakinra for COVID-19 associated sHLH. However, 2 preprints were identified. Preprints are preliminary reports of work that have not yet undergone peer review and should be considered unpublished. Preprints are usually submitted to a preprint server before or at the same time they are submitted for publication to a peer-reviewed journal. The findings reported in the preprint therefore need to be interpreted with caution and should not be reported as established information.

The first preprint was the PROSPERO systemic review ([Khan et al. 2020](#)). This systematic review did not identify any published studies of anakinra. The second preprint was a small study ([Dimopoulos et al. 2020](#)) that included 8 people with severe COVID-19 pneumonia and sHLH who were treated with anakinra. At the end of treatment with anakinra, the authors report that laboratory outcomes were improved, as was the patients' respiratory function. Two patients died. The authors conclude that anakinra may be a viable treatment for severe COVID-19 associated sHLH and note that larger clinical studies are needed to validate this concept.

A small retrospective cohort study was published after the searches for the evidence review were undertaken ([Cavalli et al. 2020](#)). It looked at the effects of anakinra in people with COVID-19, moderate to severe ARDS and hyperinflammation but hyperinflammation in the study population was not defined in the same way as sHLH ([La Rosee et al. 2019](#)).

The study found that, at 21 days, survival was 90% (26/29) in the high-dose intravenous anakinra group (5 mg/kg twice daily, median treatment duration 9 days) and 56% (9/16) in the standard treatment group ($p=0.009$). High-dose anakinra was discontinued because of adverse effects in 24% (7/29) of patients. Bacteraemia occurred in 14% (4/29) of patients receiving anakinra and 13% (2/16) of patients receiving standard treatment (p value not reported). The study by Cavalli et al. has many limitations and should be considered hypothesis-generating only.

Many trials are planned or underway to assess anakinra for treating symptoms associated with SARS-CoV-2, including several for cytokine storm syndromes and hyperinflammation, including sHLH. Primary completion is expected for the earliest of these in July 2020 (Sobi.IMMUNO-101, [NCT04324021](#) and Chatham-Cytokine Covid-19, [NCT04362111](#)).

Conclusion

Anakinra has been used (off label) for cytokine storm syndromes triggered by other viruses (such as herpes viruses), including sHLH, and is reported to be relatively well tolerated, with a favourable

safety profile. Caution is advised when using immunomodulating therapies in critically ill people with known or suspected infections because they increase the risk of infectious complications. However, it has been proposed that anakinra may be an option if such a treatment is considered necessary because it has a relatively short half-life and can be discontinued quickly if an adverse effect or concern for worsening infection arises ([Wampler Muskardin et al. 2020](#)). Anakinra can be given intravenously (off label) or subcutaneously and has a large therapeutic window. When anakinra is effective for cytokine storm syndromes, it reportedly works within 2 or 3 days ([Cron et al. 2020](#)).

See the [full evidence review](#) for more information.

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