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Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis

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Summary

Background Anakinra might improve the prognosis of patients with moderate to severe COVID-19 (ie, patients requiring oxygen supplementation but not yet receiving organ support). We aimed to assess the effect of anakinra treatment on mortality in patients admitted to hospital with COVID-19.

Methods For this systematic review and individual patient-level meta-analysis, a systematic literature search was done on Dec 28, 2020, in Medline (PubMed), Cochrane, medRxiv, bioRxiv, and the ClinicalTrials.gov databases for randomised trials, comparative studies, and observational studies of patients admitted to hospital with COVID-19, comparing administration of anakinra with standard of care, or placebo, or both. The search was repeated on Jan 22, 2021. Individual patient-level data were requested from investigators and corresponding authors of eligible studies; if individual patient-level data were not available, published data were extracted from the original reports. The primary endpoint was mortality after 28 days and the secondary endpoint was safety (eg, the risk of secondary infections). This study is registered on PROSPERO (CRD42020221491).

Findings 209 articles were identified, of which 178 full-text articles fulfilled screening criteria and were assessed. Aggregate data on 1185 patients from nine studies were analysed, and individual patient-level data on 895 patients were provided from six of these studies. Eight studies were observational and one was a randomised controlled trial. Most studies used historical controls. In the individual patient-level meta-analysis, after adjusting for age, comorbidities, baseline ratio of the arterial partial oxygen pressure divided by the fraction of inspired oxygen (PaO₂/FiO₂), C-reactive protein (CRP) concentrations, and lymphopenia, mortality was significantly lower in patients treated with anakinra (38 [11%] of 342) than in those receiving standard care or with placebo (81 [25%] of 553; adjusted odds ratio [OR] 0·37–1·41). Anakinra was not associated with a significantly increased risk of secondary infections when compared with standard care (OR 1·35 [95% CI 0·59–3·10]).

Interpretation Anakinra could be a safe, anti-inflammatory treatment option to reduce the mortality risk in patients admitted to hospital with moderate to severe COVID-19 pneumonia, especially in the presence of signs of hyperinflammation such as CRP concentrations higher than 100 mg/L (OR 0·23 [95% CI 0·12–0·43]), but not with dexamethasone co-administration (0·72 [95% CI 0·37–1·41]). Anakinra was not associated with a significantly increased risk of secondary infections when compared with standard care (OR 1·35 [95% CI 0·59–3·10]).

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Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, has affected more than 200 countries, with millions of confirmed cases and deaths worldwide.¹ The most severe and lethal forms of COVID-19 have been linked to different and possibly combined pathophysiological processes, including severe acute diffuse alveolar damage and hyaline deposits in the lungs induced by SARS-CoV-2, multiple arterial and venous thromboses resulting from both endotheliitis and hypercoagulability, and a hyperinflammatory response caused by overproduction of pro-inflammatory cytokines. Although systemically a cytokine storm might not always occur in patients,² there are clear indications of pulmonary compartmentalisation of hyperinflammation.³–⁵

To control the hyperinflammatory syndrome induced by SARS-CoV-2, in which the interleukin (IL)-1–IL-6 pathway is involved, various targeted therapies have been tested, predominantly in combination with antibiotics and anticoagulants. Anakinra, a recombinant IL-1 receptor antagonist, was selected as a logical candidate in the early days of the pandemic, since it had
Research in context

Evidence before this study
Since the emergence of the COVID-19 pandemic, numerous drugs have been administered to patients with the aim of preventing major detrimental consequences, such as respiratory and multigorgan failure and death. During the early stages of the pandemic, physicians realised that drugs aiming to regulate the host immune response might play an important role in the treatment of COVID-19. Evidence from a small number of patients with moderate or severe COVID-19 treated with anakinra, an interleukin-1 receptor antagonist, has suggested therapeutic efficacy of the drug. We systematically searched the available literature for published studies of anakinra treatment in patients admitted to hospital with COVID-19, to investigate its effect on mortality. Medline (PubMed), Cochrane, medRxiv, bioRxiv, and ClinicalTrials.gov databases were searched on Dec 28, 2020, using the terms “COVID-19” or “SARS-CoV-2” and “anakinra”, “interleukin-1”, and “interleukin blockade”.

Added value of this study
This study is, to our knowledge, the first patient-level meta-analysis to analyse the effects of anakinra treatment in patients admitted to hospital with moderate to severe COVID-19, showing a significant reduction in mortality with anakinra and also demonstrating the safety of the treatment. Most importantly, this study identifies a subgroup of patients who might benefit most from treatment with anakinra: those with C-reactive protein concentrations higher than 100 mg/L. Large, randomised controlled trials are urgently needed to further investigate the effectiveness of anakinra in this setting.

Implications of all the available evidence
Anakinra could be an effective and safe immunomodulatory treatment to prevent unfavourable outcomes in moderate-to-severe cases of pneumonia due to COVID-19. Additionally, anakinra might be helpful in avoiding adverse events, such as the secondary infections observed frequently with dexamethasone use, and could be considered as an alternative treatment option in specific subgroups (eg, patients with diabetes). Larger trials are ongoing, and their results are urgently needed to further investigate the most effective use of anakinra in the treatment of COVID-19 (ie, to establish in which patient population it is most suitable, which is the ideal biomarker to define patient status, which dose should be administered, and which is the most appropriate timepoint to administer the drug during the course of the disease).

Methods

Search strategy and selection criteria
This systematic review and patient-level meta-analysis was done according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement,19 based on a pre-specified protocol (PROSPERO: CRD42020221491). Eligibility criteria were defined with the PICO statement as follows: P=patients admitted to hospital with laboratory-confirmed SARS-CoV-2 infection; I=treatment with anakinra; C=patients receiving standard of care or placebo comparator on top of standard of care; O=mortality rate, and rate of common adverse events such as elevated liver function tests, leukopenia, and secondary infections. All randomised trials, comparative studies, and observational studies, published as full text in English were included, whereas editorials, conference abstracts, studies done in animals, case reports, and articles not written in the English language or not providing the full text were excluded. Systematic reviews were consulted for additional information, but were excluded to avoid duplication.

The search was done on Dec 28, 2020, and repeated on Jan 22, 2021, by two independent authors (EKy and EJG-B), across Medline (PubMed), Cochrane, medRxiv, bioRxiv, and ClinicalTrials.gov databases using the following terms: “COVID-19” or “SARS-CoV-2” and “anakinra”, “interleukin-1”, and “interleukin blockade”. Details of the search strategy are provided in the appendix (pp 1–2). Both reviewers assessed all articles first on the basis of the title, then on the basis of the abstract, and finally the full text to identify eligible studies. Any between-reviewer disagreements were resolved by discussion between them. Individual patient-level data were requested from investigators and corresponding authors of all eligible articles. Data from each study were first checked against reported results and queries were resolved with the investigators. Data were assessed in a consistent manner across all studies with standard definitions and variables. Data on the
following variables were collected: first author name, country of origin, publication date, study design, total number of patients, criteria for enrolment, number of patients treated with anakinra, number of controls, age and comorbidities of participants, serum ferritin and C-reactive protein (CRP) concentrations at baseline, respiratory ratio at baseline, route of anakinra administration, intake of steroids, mortality, onset of respiratory failure necessitating invasive mechanical ventilation, and onset of adverse events (elevated liver function tests, leukopenia, and secondary infections). If individual patient-level data were not available, all above available data were extracted independently by EKy and EJG-B.

The quality of each study was evaluated by EKy and EJG-B with the Newcastle-Ottawa scale. Across the entire process, between-reviewer disagreements were resolved by discussion between them.

Figure 1: Study selection

208 records identified through database searches (PubMed, Cochrane, ClinicalTrials.gov, MedRxiv, BioRxiv)

1 additional record identified through contact with researchers

209 records retrieved

31 duplicate studies removed

178 records screened for eligibility

169 records excluded

77 irrelevant title

10 case reports

5 paediatric studies

2 study protocols

2 systematic reviews

56 without intervention of interest

3 without comparator of interest

8 ongoing trials without results

9 studies for which individual patient-level data were sought

3 studies for which individual patient-level data were not provided (n=290)

6 studies for which individual patient-level data were provided (n=895)

9 studies for which aggregate data were available (n=1185)

6 studies, comprising 895 patients, included in individual patient-level meta-analysis (no patients excluded)

9 studies, comprising 1185 patients, included in aggregate data meta-analysis (no patients excluded)

9 studies for which aggregate data were not available

209 articles were identified: 208 from the initial search and one from contact with researchers. After removal of duplicates, 178 full-text articles were screened. After excluding 169 records, there were nine eligible studies for which individual patient-level data were sought. Aggregate data from these nine studies, comprising 1185 patients, were analysed, and individual patient-level data were provided for six of these studies, comprising 895 patients (figure 1). Eight studies were observational.

Role of the funding source
Sobi supported this study by providing a small research grant to cover the cost of the statistical analysis. The funder had no role in study design or conduct, data analysis, data interpretation, or in preparation of the manuscript.

Results
The primary endpoint was mortality after 28 days. For studies with a shorter follow-up, data were censored at the last observation. The secondary endpoint was safety, assessed by the rate of adverse events. Odds ratios and their respective 95% CIs were used to compare anakinra-treated patients to control groups for each endpoint. Pre-defined subgroup analyses were done for the primary endpoint according to the following variables: the baseline ratio of the arterial partial oxygen pressure divided by the fraction of inspired oxygen (PaO₂/FiO₂), baseline CRP and serum ferritin concentrations, and the Charlson Comorbidity Index. A logistic regression analysis was done: first, to detect any interaction effect of anakinra treatment with the different studies; and second, to detect whether the effect of anakinra on the primary outcome remained independent of factors interfering with mortality (ie, age, Charlson comorbidity index, CRP, and PaO₂/FiO₂). Predefined cutoffs were used for characterisation of the above subgroups. Sensitivity analyses were planned for time period (ie, before and after implementation of dexamethasone) and for randomised controlled trials. Meta-analysis of aggregate data was done by the Mantel-Haenszel method. The Sidik-Jonkman estimator was used for $\tau^2$ and the Q-profile method used for the confidence interval of $\tau^2$ and $\tau$. A continuity correction of 0–1 was applied in studies with zero cell frequencies. Finally, heterogeneity and inconsistency were assessed in a meta-analysis of aggregate data from all eligible studies using the $I^2$ criterion. The fixed-effects model was used for $I^2$ less than 50%, and the random-effects model used for $I^2$ 50% or greater. The corresponding forest plot was produced, and publication bias was assessed with the funnel plot. Studies without available individual patient-level data were only included in the aggregate data meta-analysis. No imputation was made for missing data within individual patient-level data. All statistical analyses were done with SPSS (version 23) and Review Manager (version 5.3).
(either prospective or retrospective) and only one was a randomised controlled trial.\textsuperscript{24} 103 (12%) of 895 patients were on mechanical ventilation at baseline. Among the three studies for which individual patient-level data were not obtained,\textsuperscript{23,30} two favoured anakinra treatment\textsuperscript{27,30} and one did not.\textsuperscript{24} Characteristics of the included studies are summarised in table 1. Three studies were done in France,\textsuperscript{22–24} three in Italy,\textsuperscript{25–27} one in the Netherlands,\textsuperscript{28} one in Greece,\textsuperscript{29} and one in Oman.\textsuperscript{30} Data published during the early period of the pandemic in an Italian study\textsuperscript{31} were prospectively recruited both anakinra-treated and control patients after implementation of dexamethasone into standard of care.\textsuperscript{27} In another study, methylprednisolone was part of the intervention as it was co-administered with anakinra.\textsuperscript{30} Mortality data after 28 days were available from seven studies, whereas data were censored at the last observation in two studies\textsuperscript{23,30} with a shorter follow-up. An assessment of the individual risk of bias according to the Newcastle-Ottawa scale is provided in the appendix (p 5). The overall quality of included studies was high. Aggregate data from nine studies, comprising 1185 patients (509 on anakinra and 676 controls), showed a significant reduction in mortality among anakinra-treated patients compared with patients receiving standard of care with or without placebo; the pooled odds ratio (OR) for mortality was 0·37 (95% CI 0·27–0·51; \(I^2\) 31%), as shown in figure 2. There was no evidence of publication bias (test for funnel plot asymmetry: \(t=–0·9137, p=0·39\); appendix p 6). In the individual patient-level meta-analysis,

### Table 1: Characteristics of included studies

| Study type; individual patient data available? | Study setting and period | Inflammation criteria for inclusion | Number of patients | Route of administration | Steroid intake |
|---|---|---|---|---|---|
| yes | France: not mentioned | CRP >110 mg/L | 12 | Anakinra group | No dexamethasone as standard of care; no other steroids |
| yes | France: March, 2020 (historical controls); March 24–April 6, 2020 (anakinra group) | CRP >25 mg/L | 59 | Intravenous | Desmethylasone in 1 of 59 in anakinra group; other glucocorticoids in 6 of 59 in anakinra group, and 8 of 55 in control group |
| yes | France: April 8-26, 2020 | CRP >100 mg/L or ferritin >1000 µg/L, or both | 65 | Subcutaneous; intravenous if on invasive mechanical ventilation | No dexamethasone as standard of care; methylprednisolone co-administered with anakinra |
| yes | Italy: Feb 25–March 30, 2020 | CRP >100 mg/L or ferritin >900 µg/L | 62 | Intravenous | Desmethylasone in 54 of 275 controls and in 7 of 62 in anakinra group |
| no | Italy: March 10–17, 2020 (historical controls); March–May, 2020 (anakinra group) | CRP or ferritin >3 times the normal limits | 63 | Intravenous | No dexamethasone as standard of care; methylprednisolone in 33 of 63 patients in anakinra group |
| yes | Netherlands: March 11–April 27, 2020 | Ferritin >1800 µg/L; clinical hyperinflammation signs (persistent fever, unexplained progression of multorgan failure) | 21 | Intravenous | Desmethylasone in 14 of 39 patients on standard of care and in 3 of 21 in anakinra group |
| yes | Greece: April 16–Sept 12, 2020 | suPAR >6 µg/L | 130 | Subcutaneous | Desmethylasone as standard of care in 47 of 120 controls and in 52 of 130 in anakinra group |
| no | Oman: April 1–June 14, 2020 (historical controls); June 15–July 25, 2020 (anakinra group) | no | 45 | Subcutaneous | Desmethylasone in 24 of 45 in anakinra group, and 3 of 24 controls; methylprednisolone in 1 of 45 in anakinra group, and in 23 of 24 controls |

CRP=C-reactive protein. suPAR=soluble urokinase-type plasminogen activator receptor.
comprising 895 patients. 38 (11%) of 342 anakinra-treated patients died versus 137 (25%) of 553 patients receiving standard of care with or without placebo (OR 0·38 [95% CI 0·26–0·56]; p=0·0001; table 2). No interaction effect was observed among the six studies and anakinra treatment for the primary outcome (p=0·15; table 2). After adjusting for age, comorbidities, baseline PaO₂/FiO₂, lymphopenia and CRP concentrations, anakinra was shown to independently protect against mortality (adjusted OR 0·32 [95% CI 0·20–0·51]; p<0·0001; table 2). Similar ORs were estimated for anakinra treatment after adjustment for ferritin (data available for 486 patients; adjusted OR 0·35 [95% CI 0·23–0·52]; p<0·0001) and IL-6 concentrations (data available for 530 patients; OR 0·40 [0·33–0·48]; p=0·01). The predefined sensitivity analyses for randomised controlled trials were not possible, since only one randomised controlled trial was included in this meta-analysis.

The mortality reduction associated with anakinra treatment was significant in the absence of dexamethasone co-administration (559 patients; OR 0·23 [95% CI 0·12–0·43]), but not with co-administration of dexamethasone (239 patients; OR 0·72 [0·37–1·41]; pBreslow=0·012). Similarly, this beneficial effect of anakinra was significant in patients breathing spontaneously at baseline (792 patients; OR 0·30 [95% CI 0·19–0·48]) but not in the smaller subgroup of those who were mechanically ventilated at baseline (103 patients; OR 0·52 [0·20–1·36]; pBreslow=0·45). Subgroup analyses adjusting for CRP and ferritin concentrations and baseline PaO₂/FiO₂ showed that anakinra was more effective in lowering mortality in patients presenting with CRP concentrations higher than 100 mg/L (OR 0·28 [95% CI 0·17–0·47]), but the therapeutic efficacy of anakinra did not appear to be related to baseline ferritin concentrations or baseline PaO₂/FiO₂ (figure 3). In a subgroup analysis of 116 patients with diabetes and 299 patients without diabetes, the effect of anakinra on mortality was similar in both groups (OR 0·40 [95% CI 0·17–0·91] vs 0·37 [0·19–0·74]; pBreslow=0·90).

The safety of anakinra was investigated as a secondary endpoint. Anakinra treatment was associated with elevation of liver function tests (pooled OR 3·00 [95% CI 0·36–34·66]; P 85%), as well as onset of leukopenia (3·71 [0·49–27·84]; P 51%) and secondary infection (1·35 [0·59–3·10]; P 79%; appendix p 7). Thromboembolic events were reported in only two studies;2123 thus, no meta-analysis was done for this endpoint. Nevertheless, in both studies, anakinra did not increase the thromboembolic risk compared to standard-of-care treatment or placebo, or both.

**Discussion**

The results of this systematic review and meta-analysis indicate that, in patients admitted to hospital with pneumonia due to COVID-19, treatment with anakinra reduces mortality when compared with standard of care, with or without placebo. This survival benefit was most
profound in patients with hyperinflammation and CRP concentrations higher than 100 mg/L. We also observed a non-significant increase in the risk of adverse events with anakinra.

Identifying and preventing unfavourable outcomes in patients with COVID-19 is a real challenge. Algorithms have been constructed and validated, taking into account various clinical variables, including older age, male sex, high body-mass index, and comorbidities. Markedly lymphopenia and elevated inflammatory biomarkers such as ferritin, IL-6, and CRP were first shown to be associated with severe disease in early reports of patients with COVID-19. IL-6 is a potent stimulator of CRP production by the liver. Therefore, CRP concentrations probably represent the simplest biological test to indirectly evaluate the intensity of ongoing inflammation and a signal indicating a window of opportunity for targeted immunotherapy. Our results show a profound benefit of anakinra in patients with CRP concentrations higher than 100 mg/L.

Some patients with severe COVID-19 develop a hyperinflammatory phenotype known as a cytokine storm. Cytokine storm syndrome is a life-threatening condition requiring intensive care and with a high mortality rate, characterised by overwhelming systemic inflammation, with hyper-ferritinaemia, haemodynamic instability, and multiorgan failure. The trigger for cytokine storm syndrome might be extensive cell death, resulting in massive release of pro-inflammatory intracellular mediators and danger signals, notably including IL-1α. These intracellular mediators in turn induce an uncontrolled immune response with continuous activation and expansion of immune cells, which produce large amounts of other pro-inflammatory cytokines such as IL-1β, IL-6, and IL-18, as well as interferon-γ (IFNγ) and tumour necrosis factor (TNF). Not all patients experience a cytokine storm, but even in those who do not, the pulmonary inflammatory response can be exacerbated and these patients might benefit from immunomodulating therapies.

IL-1 is located upstream of IL-6 in the inflammation cascade, and such a hierarchical process could explain why targeting IL-1 appears to be more efficient in hyperinflammatory forms of COVID-19 than IL-6 inhibition, which has already provided encouraging results in randomised controlled trials of patients with severe COVID-19 admitted to the intensive care unit. Dexamethasone was the first immune modulator to show a clear survival benefit when administered to patients admitted to hospital with COVID-19 in need of oxygen supplementation in the RECOVERY trial; thus, after July, 2020, dexamethasone was incorporated into the standard of care for patients admitted to hospital with COVID-19.

The cohort studies included in the current analysis of anakinra in patients with COVID-19 were not randomised and included patients receiving usual care as historical controls, mainly before implementation of dexamethasone as standard of care. Although the cohort design clearly has its limitations, the observed magnitude of the protective effect of anakinra was convincing enough to continue with additional studies, such as the open-label single-arm prospective SAVE study, which concluded that soluble urokinase-type plasminogen activator receptor (suPAR)-guided anakinra treatment prevented onset of respiratory failure necessitating mechanical ventilation and reduced mortality. The only randomised controlled trial completed so far was initiated by the French consortium CORIMUNO. It did not replicate the results observed in observational studies, and was prematurely interrupted because of

| CRP (mg/L) | 28-day mortality | Odds ratio (95% CI) | pinteraction |
|-----------|------------------|---------------------|--------------|
| <100      | 30/186 (16%)     | 15/131 (11%)        | 0·67 (0·35–1·31) |
| >100      | 107/364 (29%)    | 22/208 (11%)        | 0·28 (0·17–0·47) |

| Ferritin (ng/mL) | 28-day mortality | Odds ratio (95% CI) |
|------------------|------------------|---------------------|
| <1000            | 17/110 (15%)     | 25/137 (12%)        |
| >1000            | 21/101 (31%)     | 19/138 (14%)        |

| CCI             | 28-day mortality | Odds ratio (95% CI) |
|-----------------|------------------|---------------------|
| ≤2              | 12/208 (8%)      | 4/156 (3%)          |
| >2              | 112/296 (38%)    | 27/153 (18%)        |

| PaO₂/FiO₂      | 28-day mortality | Odds ratio (95% CI) |
|----------------|------------------|---------------------|
| <100           | 72/350 (21%)     | 19/217 (9%)         |
| >100           | 42/95 (44%)      | 18/109 (17%)        |

Figure 3: Subgroup analysis of mortality in patients treated with anakinra versus those treated with standard of care

| Outcome | Standard of care | Anakinra | Odds ratio (95% CI) | pinteraction |
|---------|------------------|----------|---------------------|--------------|
| CRP     | ≤100             | >100     | 0·67 (0·35–1·31)    | 0·04         |
| Ferritin| ≤1000            | >1000    | 0·67 (0·32–1·42)    | 0·21         |
| CCI     | ≤2               | >2       | 0·53 (0·21–1·31)    | 0·44         |
| PaO₂/FiO₂| ≤100            | >100     | 0·37 (0·22–0·63)    | 0·36         |
|         | ≤100             | >100     | 0·25 (0·13–0·48)    |              |

*p values of the interaction effect of the treatment on mortality, in each subgroup and among the studies are provided. CRP=C-reactive protein. CCI=Charlson comorbidity index. PaO₂/FiO₂=ratio of the arterial partial oxygen pressure divided by the fraction of inspired oxygen.
assumed futility, suggesting that anakinra was not effective in reducing the need for non-invasive or mechanical ventilation or in preventing deaths in patients with COVID-19 and mild to moderate pneumonia. However, the 14-day mortality rate was 15% in the anakinra group compared to 24% in the usual care group, and the WHO Clinical Progression Scale was also suggestive of a beneficial effect of anakinra at day 14. Unfortunately, stopping for futility increases the risk of imbalance in prognostic factors and leaves the primary research question unanswered, especially when the decision to stop early does not follow a pre-specified stopping boundary. Additionally, the cutoff criterion chosen for CRP in the CORIMUNO study was relatively low (>25 mg/L), which suggests that a proportion of patients were not in the hyperinflammatory phase of COVID-19, during which anakinra is probably the most effective.

In the present analysis, in contrast to published evidence supporting a synergistic effect of dexamethasone with IL-6 inhibition, we did not observe a significant survival benefit of anakinra when co-administered with dexamethasone. For patients already under mechanical ventilation at the start of treatment, anakinra similarly did not show a significant survival benefit. However, decreased statistical power due to the small number of patients included in these subgroups probably contributed to these outcomes. It cannot be ruled out that anakinra has no additional benefit when co-administered with dexamethasone, or if anakinra is given too late, when severe organ failure is already apparent and organ support is needed. However, anakinra might be a safer alternative to dexamethasone when considering the risk of secondary infections, which was low in early reports but might rise after more widespread use of dexamethasone. An additional benefit might be seen in specific populations, such as patients with diabetes, who are more susceptible to secondary infections and less likely to tolerate hyperglycaemia. Indeed, our study showed a similar risk of secondary infections in the anakinra group compared with the control group, and a survival benefit of anakinra in a subgroup of patients with diabetes.

To the best of our knowledge, this is the first patient-level meta-analysis to investigate the effect of anakinra treatment in patients admitted to hospital with COVID-19, showing a significant reduction in mortality with anakinra, and characterising a subgroup of patients (those with CRP >100 mg/L) as the best candidates for this treatment. The main limitations of this meta-analysis are the retrospective observational design of the majority of studies included, raising concerns about bias and possible confounders among the compared groups, as well as the fact that most of the studies were done before dexamethasone was incorporated into standard-of-care treatment of patients admitted to hospital with COVID-19. Larger randomised trials are urgently needed to clarify the place of anakinra in the anti-COVID19 armamentarium; ongoing trials (appendix pp 3–4) include the REMAP-CAP trial (an international, multifactorial, adaptive platform randomly assigning patients to tocilizumab or sarilumab or anakinra or standard of care and comparing in-hospital mortality and days free of organ support to day 21 among the groups), and the placebo-controlled randomised controlled trial SAVE-MORE (NCT04680949) in Greece and Italy, comparing 28-day outcomes with anakinra versus placebo in patients already receiving standard-of-care treatment for COVID-19.

Declaration of interests

EJG-B has received honoraria from AbbVie USA, Abbott CH, Biotest Germany, Brahms, InfaRx, MSD Greece, XBiotech, and Angelini Italy; independent educational grants from AbbVie, Abbott CH, Astellas Pharma Europe, AxisShield, bioMérieux, InfaRx, the Medicines Company, and XBiotech; and funding from the FrameWork 7 program HemoSpec (granted to the National and Kapodistrian University of Athens), the Horizon2020 Marie-Curie Project European Sepsis Academy (granted to the National and Kapodistrian University of Athens), and the Horizon 2020 European Grant ImmunoSep (granted to the Hellenic Institute for the Study of Sepsis); MG has received speakers’ fees and unrestricted grants from Novartis and Sohi. PP, M Ko, and E Ko are funded by a COVID-19 grant paid to the Radboud University Medical Center (Radboudumc). JE-O is a co-founder, shareholder, and CSO of ViroGates, Denmark, and named inventor on patents on suPAR owned by Copenhagen University Hospital Hvidovre, Denmark. GK has received from ROCHE-CHUGA Research Grants (~€200,000), fees from Sohi France for scientific presentations (~€6000) and participated in a SOBI Advisory Board on COVID (unpaid) and in an OLATEC Monitoring Board (unpaid). GCa has received speakers’ and consulting fees from Novartis and Sohi. LD has received grants (paid to LD’s institution outside the current work) from AbbVie, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Kiniksa, Merd Sharp & Dohme, Mundipharma Pharmaceuticals, Novartis, Pfizer, Roche, Sanofi Genzyme, and Sohi; and consulting fees from AbbVie, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Galapagos, GlaxoSmithKline, Kiniksa, Novartis, Pfizer, Roche, Sanofi-Genzyme, and Sohi. GH reports consultancy fees from Bristol-Myers Squibb, Lilly, Novartis; speakers’ fees from AbbVie, Bristol-Myers Squibb, Celgene, Lilly, Novartis, Pfizer, Roche, Sanofi-Aventis; support for attending meetings from Bristol-Myers Squibb, Fresenius-Kabi, Janssen-Cilag, Lilly, Mylan, Roche, UCB; and participation on advisory boards for Bristol-Myers Squibb and Lilly. FV has received (via the Institut de Recherche pour le Développement) Horizon 2020-EDCTP-European Grants: PANDORA and ITAIL-COVID. All other authors declare no competing interests.

Data sharing

Data collected for this study, including de-identified individual participant data, will be made available following publication. Requests for data can be made to the corresponding author, outlining specific data needs, analysis plans and dissemination plans. These requests will be reviewed by a steering committee of the International Collaborative Group for Anakinra in COVID-19. Data will be shared after a data access agreement is signed, for any proposed purpose approved by the steering committee and all data will be de-identified and protected health information stripped.
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