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SYSTEMATIC REVIEW

Anakinra for patients with COVID-19: an updated systematic review and meta-analysis

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Abstract

Severe COVID-19 patients can develop a maladaptive immune response with hyper-production of cytokines and chemokines which lead to alveolar damage, endothelial activation, coagulopathy and thromboembolic events. We performed a meta-analysis which included any study performed on COVID-19 patients with respiratory hypoxemic failure who received anakinra versus any comparator. Primary endpoint was mortality. Secondary endpoints were intubation rate, superinfection and thromboembolic events. Subgroups analyses included patients in general ward, with hyperinflammation and/or baseline ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2) >200. Twenty-four studies were included. Mortality in anakinra patients was significantly lower than mortality of controls (19% *vs.* 28%; $p < 0.0001$). Anakinra patients had significantly lower risk of intubation (16% *vs.* 33%; $p < 0.001$). Mortality reduction was confirmed in general ward settings, in patients with hyperinflammation and with PaO_2/FiO_2 >200, but not when selecting randomized studies only. A trend towards increased mortality in more severe patients was observed.

Keywords

Anakinra; COVID-19; SARS-CoV-2; Meta-analysis; Mortality

1. Introduction

The COVID-19 pandemic, caused by the spread of the severe acute respiratory syndrome coronavirus (SARS-CoV)-2, has affected more than 200 countries worldwide with millions of confirmed cases and deaths [1].

A subgroup of patients with severe COVID-19 develop a hyper-inflammatory, maladaptive immune response to the virus, often associated with excess cytokine and chemokine production, massive influx of inflammatory cells into the lung leading to acute and diffuse alveolar damage with hyaline deposits, and endothelial activation with coagulopathy leading to thromboembolic events [2, 3]. Given the high mortality of severe COVID-19, and the role of excess or aberrant cytokine production in the pathogenesis of this condition, treatment with available biologic agents or targeted inhibitors of cytokines emerged as a logical therapeutic opportunity [4–7]. Following early reports indicating that SARS-CoV-2 activates the NLR family pyrin domain containing 3 (NLRP3) inflammasome and prompts the release of the pivotal pro-inflammatory cytokine IL-1 [8], several studies evaluated targeted inhibition of this cytokine for the treatment of COVID-19. The first-in-class inhibitor of IL-1 is anakinra, a recombinant form of the naturally occurring interleukin (IL)-1 receptor antagonist, which is approved for the treatment of rheumatoid arthritis and used off label to treat a variety of inflammatory diseases [9, 10]. Of note, anakinra had been previously tested with encouraging results and no safety concerns in other conditions exhibiting similarities with severe COVID-19, including macrophage activation syndrome or the cytokine release syndrome developing during chimeric antigen receptor (CAR)-T cell therapy [11, 12].

Early during the pandemic, multiple retrospective studies and case series of patients with severe COVID-19 treated with anakinra reported promising results [13–18], which were confirmed in an early meta-analysis [19]. These findings paved the way for additional larger studies, including controlled investigations which confirmed the benefit of anakinra treatment [20]. In most studies, anakinra was administered in severe patients with signs of hyperinflammation and was associated with some degree of clinical effectiveness; however, some investigators found less encouraging results [21].

Since larger studies were recently published on this topic, in this systematic review and meta-analysis, we evaluate all available evidence on the effectiveness of anakinra for the treatment of COVID-19 with the aim to determine whether this targeted immunotherapy might reduce mortality or need for Intensive Care Unit (ICU) level care, and to determine a specific candidate population, which is particularly likely to benefit from this treatment.

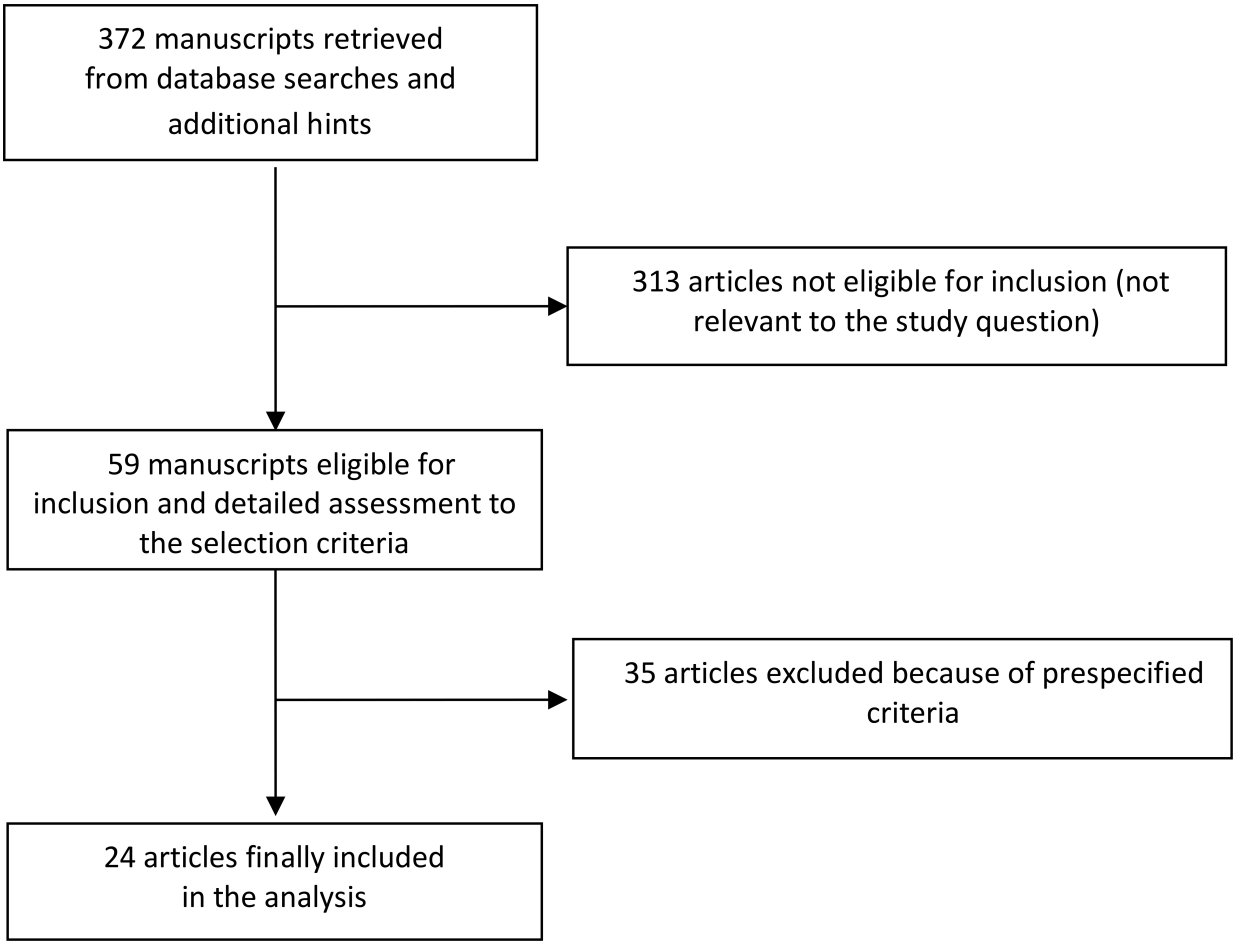

FIGURE 1. Flow diagram for selection of articles.

2. Material and methods

2.1 Search strategy

Pertinent articles were separately searched in different databases (PubMed, medRxiv, bioRxiv, Embase, BioMedCentral, and the Cochrane Central Register of Controlled Trials (CENTRAL) by two investigators (LP, GL). No date restrictions were applied. Last search update was performed in March 2022. The full PubMed search strategy aimed to find all studies ever performed with anakinra in COVID-19 patients (**Supplementary material**). Moreover, researchers looked through references of collected papers and relevant reviews and contacted international expert for additional studies. No language restriction was applied.

2.2 Study selection and data abstraction

Titles and abstracts of retrieved references were separately studied by two researchers (LP; GL) and dissensus was solved by agreement or ruling of a third author (GC). If appropriate, references were deepened as full-text. The following PICOS criteria were used: (P) hospitalized adult patients with COVID-19; (I) anakinra; (C) standard care, any drugs, placebo; (O) at longest follow-up mortality (primary outcome), need for endotracheal intubation and invasive mechanical ventilation, occurrence of bacterial superinfection, occurrence of markedly elevated serum transaminases, occurrence of thromboembolism; (S) prospective studies, retrospective cohort studies, randomized clinical trials.

Exclusion criteria were paediatric studies, duplicate or overlapping publications, case-report, and studies not reporting data on primary outcome.

After identifying the studies meeting the PICOS criteria, study details and patients' baseline, procedural and outcome were individually collected by two researchers. Disagreements were solved by consensus or by arbitration of another researcher. If fundamental data were missing, at least two requests for additional data were sent by e-mail to the corresponding author.

2.3 Assessment of risk of bias in included studies

The Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) scale was used to evaluate the risk of bias of non-randomized studies [22, 23], while the internal validity and risk of bias of randomized trials was evaluated according to the Risk of Bias (RoB) 2 Tool [23, 24]. Divergences were solved by discussion.

2.4 Data analysis and synthesis

We followed The Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [23, 25] and was registered on PROSPERO

(CRD42020196808).

Computations were performed with Review Manager (RevMan) (Computer program). Version 5.4, The Cochrane Collaboration, 2020 and R software version 4.0.5 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/). The Cochran Q test was used to measure statistical heterogeneity and statistical significance was fixed at 0.10 (for a two-tailed test). I^2 = 100% X (Cochran's Q, heterogeneity statistic-degrees of freedom) was used to calculate Statistical consistency.

Dichotomous outcomes from individual studies were computed to quantify single and pooled risk ration (RR) with pertinent 95% confidence interval (CI), by means of inverse variance method. If I^2 was less than, equal or greater than 25% a fixed or random-effect model were respectively applied. Zero events in both groups were computed by applying a continuity correction (adding one to each group value).

Sensitivity analyses were performed by removing in succession every single study and analysing the remaining dataset and including only randomized clinical trials.

Four subanalyses were performed: (1) on studies performed in ICU versus general ward setting; (2) on studies with or without hyperinflammation as inclusion criteria; (3) on studies including patients with baseline $PaO_2/FiO_2 \leq$ or >200; (4) on studies where anakinra was administered subcutaneously or intravenously.

Statistical significance was fixed at 0.05 level. Reported *p* values were unadjusted.

3. Results

3.1 Study characteristics

Different databases searched identified a total of 372 articles. After excluding 313 duplicate or non-pertinent titles or abstracts, 59 studies were examined as full text according to the selection criteria (Fig. 1). Thirty-five studies were further excluded according to our prespecified exclusion criteria (Fig. 1).

The 24 manuscripts finally included involved 5933 patients (2025 received anakinra and 3908 received control treatment) [13, 14, 18, 21, 26–45] (Table 1). More information about included studies is available in Table 1 (Table 1). Only five randomized clinical trials (RCTs) were identified [21, 32, 35, 37, 39] including one preprint article [32] while most studies were retrospective [13, 14, 18, 27, 33, 34, 36, 40, 43], five were prospective [29–31, 38, 44] and four were prospective with historical controls [26, 41, 42, 45].

Main clinical difference was ascribable to inclusion criteria, setting, duration of study drug administration and control treatment (Table 1). Most studies included only patients with hyperinflammation [13, 14, 18, 27–29, 31, 35, 37, 39, 40, 42, 43], while hyperinflammation was not an inclusion criterion in ten articles [21, 26, 32–34, 36, 38, 41, 44, 45]. Anakinra was usually administered in general ward setting, with only four studies performed in ICU [29, 31, 35, 46] and six which included both general ward and critically ill patients [14, 27, 34, 38, 42, 45]. Comparators were standard care or standard care plus tocilizumab in most cases (Table 1).

Overall risk of bias of included studies was high (**Supplementary material**).

3.2 Quantitative data synthesis

3.2.1 Primary outcome

Overall mortality at the longest available follow-up of patients who received anakinra was significantly lower than mortality of patients in the control group (384/2025 (19%) in the anakinra group *vs.* 1107/3908 (28%) in the control group, RR = 0.69 (95% CI 0.54 to 0.87), $p < 0.0001$, $I^2 = 70\%$) (Table 2; Fig. 2).

Sensitivity analysis performed by removing in succession every single study and analysing the remaining dataset confirmed the above results. On the contrary, when including only randomized clinical trials results were not confirmed (Table 2; **Supplementary material**). Visual inspecting of funnel plot excluded bias related to the presence of small publication (Fig. 3).

3.2.2 Subgroup analysis on primary outcome

Mortality of patients who received anakinra was lower than mortality of patients who received control treatment in general ward setting (146/1296 (11%) in the anakinra group *vs.* 327/1684 (19%) in the control group, RR = 0.66 (95% CI 0.47 to 0.93), *p* for effect = 0.02, I^2 = 61%). On the contrary, there was a trend toward an increased mortality in critically ill patients who received anakinra in ICU (161/424 (38%) in the anakinra group *vs.* 656/1934 (34%) in the control group, RR = 1.14, 95% CI 0.99 to 1.30, *p* for effect = 0.06, $I^2 = 0\%$) (Table 2; **Supplementary material**).

A statistically significant reduction in mortality was observed in studies including patients with hyperinflammation (150/1131 (13%) in the anakinra group *vs.* 355/1609 (22%) in the control group, RR = 0.70, 95% CI 0.54 to 0.90, *p* for effect = 0.006, I^2 = 45%) and in studies including patients with baseline $PaO_2/FiO_2 >200$ (54/811 (7%) in the anakinra group *vs.* 117/597 (20%) in the control group, RR = 0.68, 95% CI 0.50 to 0.93, *p* for effect < 0.001, $I^2 = 11\%$) (Table 2; **Supplementary material**).

Mortality reduction was confirmed only in studies in which anakinra was administered subcutaneously (149/1139 (13%) in the anakinra group *vs.* 257/1266 (20%) in the control group, RR = 0.66, 95% CI 0.47 to 0.91, *p* for effect = 0.01, $I^2 = 61\%$) (Table 2; **Supplementary material**).

3.2.3 Secondary outcomes

Patients who received anakinra presented a lower risk of need for intubation than controls (202/1242 (16%) in the anakinra group *vs.* 606/1856 (33%) in the control group, RR = 0.57 (95% CI 0.41 to 0.79), *p* for effect < 0.001, $I^2 = 66\%$) (Table 2; **Supplementary material**).

Incidence of superinfection, thromboembolic events and elevated serum transaminases did not differ between groups (Table 2; **Supplementary material**).

TABLE 1. Description of the studies included in the meta-analysis.

First author	Year	Study design	Setting	Inclusion criteria	Mean baseline PaO_2/FiO_2	Anakinra patients	Control patients	Anakinra dosage	Concomitant treatments	Comparator	Follow-up
Aomar-Millán IF [40]	2021	Retrospective	Ward	Severe COVID-19 pneumonia and hyperinflammation.	Not reported	10	133	On the first day 100 mg/6–12 h. On the second day, all patients received 100 mg/12 h from day 2 to day 6.	Hydroxychloroquine, azithromycin lopinavir/ritonavir, ceftriaxone, bemiparin, intravenous methylprednisolone 2 mg/kg/day for 3 days (if hyperinflammation)	Methylprednisolone alone or with tocilizumab	60 days
Balkhair A [41]	2021	Prospective, open label, interventional with historical controls	Ward	Severe COVID-19 pneumonia	117.5 (7.78)	45	24	Subcutaneous, 100 mg twice daily for 3 days, followed by 100 mg daily for a maximum of 7 days.	Ceftriaxone or piperacillin-tazobactam, macrolide and thromboembolic prophylaxis Some patients in the interventional arm received a maximum of three doses of intravenous dexamethasone (6 mg per day) before enrollment. Many historical controls received a 5-day course of intravenous methylprednisolone (40 mg twice per day for 5 days).	Standard care	Hospital stay
Bozzi G [42]	2021	Prospective, observational with historical controls	Ward and ICU	Patients with respiratory failure (intubated and non-intubated) and hyperinflammation	151 (78.58)	65	55	Subcutaneous, 200 mg/8 h for 3 days, then 100 mg/8 h up to day 14. Patients on MV were treated with intravenous administration	Metilprednisolone, remdesivir, hydroxychloroquine lopinavir/ritonavir, anticoagulant therapy	Standard care	28 days

TABLE 1. Continued.

First author	Year	Study design	Setting	Inclusion criteria	Mean baseline PaO_2/FiO_2	Anakinra patients	Control patients	Anakinra dosage	Concomitant treatments	Comparator	Follow-up
Cauchois R [43]	2020	Retrospective	Ward	Pneumonia and hyperinflammation	Not reported	12	10	Intravenous, 300 mg for 5 days, then 200 mg/die for two days, and then 100 mg/die for one day	Antibiotics and hydroxychloroquine,	Standard care	20 days
Cavalli G [10]	2021	Retrospective	Ward	ARDS and hyperinflammation	Not reported	62	330	intravenously 10 mg/kg per day	Hydroxychloroquine, antiviral drug, empirical antibiotic, methylprednisolone	Standard care alone or with IL-6 inhibitors	Hospital stay
CORIMUNO-ANA-1 trial [21]	2021	RCT	Ward	Mild-to-moderate COVID-19 pneumonia	Not reported	59	57	200 mg twice a day (day 1–3), 100 mg twice (day 4), 100 mg once on day 5	Antibiotics, antivirals, corticosteroids, vasopressors, anticoagulants	Standard care	14 days
Dalekos GN [44]	2021	Prospective	Ward	Mild-to-moderate COVID-19 pneumonia	295 (178)	213	213	2–8 mg/kg/day in 1–3 doses subcutaneously or intravenously	Enoxaparin and antibiotics, hydrocortisone or dexamethasone	Standard care	30 days
Declercq J [37]	2021	RCT	Ward	Bilateral infiltrates, PaO_2/FiO_2 <350, cytokine release.	144.5 (145)	112	230	anakinra 100 mg once daily subcutaneously for 28 days or until hospital discharge	Hydroxychloroquine and/or dexamethasone	Standard care and/OR IL-6 inhibitors	28-days
de la Calle C [45]	2021	Prospective with historical controls	Ward and ICU	Severe pneumonia, anakinra as rescue therapy after no success with tocilizumab	94 (69)	20	20	Subcutaneous, 100 mg/12 h on day 0, then at 100 mg/24 h from day 1 to day 5.	Supportive care with or without oral lopinavir-ritonavir, hydroxychloroquine, azithromycin, subcutaneous interferon-β, corticosteroids and antibiotics	Tocilizumab	Hospital stay
ESCAPE trial [38]	2021	Prospective	Ward and ICU	ARDS, and macrophage activation syndrome	156 (118)	60	42	Intravenously, 200 mg/8hfor seven days	Antibiotics, hydroxychloroquine, remdesivir, dexamethasone	Tocilizumab	28 days

TABLE 1. Continued.

First author	Year	Study design	Setting	Inclusion criteria	Mean baseline PaO_2/FiO_2	Anakinra patients	Control patients	Anakinra dosage	Concomitant treatments	Comparator	Follow-up
Franzetti M [27]	2021	Retrospective	Ward and ICU	Respiratory failure (CPAP or intubated) and hyperinflammation	133 (34.1)	56	56	Subcutaneous, 200 mg/6 h for 7 days. Patients on MV were treated with intravenous administration	Lopinavir/ritonavir, hydroxychloroquine a first-line antibiotic therapy, enoxaparin	Standard care	28 days
García-García JA [36]	2021	Retrospective	Ward	Adult patients with mild-to-moderate COVID-19 pneumonia	Not reported	125	217	Anakinra subcutaneously at a standard dose of 200 mg twice on the first day, followed by 100 mg twice daily until a course of 10 days	Corticosteroids, anticoagulants +/− antivirals	Standard care plus baricitinib	Hospital stay
Huet T [26]	2020	Prospective with historical controls	Ward	Adult patients with severe COVID-19-related bilateral pneumonia	Not reported	52	44	Subcutaneous, 100 mg twice daily for 72 h, followed by 100 mg daily for 7 days.	Hydroxychloroquin, oral azithromycin, parenteral β-lactam antibiotics, thromboembolic prophylaxis. Some patients received an iv bolus of methylprednisolone	Standard care	Hospital stay
Iglesias-Julián E [28]	2020	Retrospective	Ward	Adult patients with COVID-19 ARDS and hyperinflammation	193 (137.88)	9	18	Subcutaneous, 100 mg/6 h for at least 3 days. Afterwards, dosage eventually reduced to every 24 h up to 7 days.	Antibiotics, hydroxychloroquine, methylprednisolone	Tocilizumab	Hospital stay
Kharazmi AB [35]	2022	RCT	ICU	Elevated C-reactive protein, PaO_2/FiO_2 <300	Not reported	15	15	Intravenous 100 mg anakinra once daily	Remdesivir, lopinavir/ritonavir, interferon, favipiravir, and corticosteroid, antibiotics	Standard care	Hospital stay

TABLE 1. Continued.

First author	Year	Study design	Setting	Inclusion criteria	Mean baseline PaO_2/FiO_2	Anakinra patients	Control patients	Anakinra dosage	Concomitant treatments	Comparator	Follow-up
Kooistra EJ [29]	2020	Prospective	ICU	Mechanically ventilated patients with ARDS and hyperinflammation	139 (50.41)	21	39	Intravenous anakinra 300 mf, followed by 100 mg every 6 h.	Corticosteroids, remdesivir, cloroquine	Standard care	28 days
Kyriazopoulou E [30]	2021	Prospective	Ward	Severe COVID-19 pneumonia and hyperinflammation	277 (115.6)	130	179	Subcutaneous, 100 mg once daily for 10 days	Antibiotics, hydroxychloroquine, remdesivir, dexamethasone	Standard care	30 days
SAVE-MORE trial [39]	2021	RCT	Ward	Severe COVID-19 pneumonia and hyperinflammation	230 (85.99)	405	189	Subcutaneous, 100 mg once daily for 10 days	Antibiotics, hydroxychloroquine, remdesivir, dexamethasone, thromboembolic prophylaxis	Placebo	28 days
Langer-Gould A [34]	2020	Retrospective	Ward and ICU	Mild-to-severe COVID-19 pneumonia	Not reported	41	52	Subcutaneous, 100 mg/6 h	Antibiotics, hydroxychloroquine, remdesivir, dexamethasone	Tocilizumab	Hospital stay
Monti G [31]	2021	Prospective	ICU	Mechanically ventilated patients with ARDS, and hyperinflammation	Not reported	15	46	Intravenously, at a dose of 10 mg/kg per day	No corticosteroids treatment was allowed with anakinra or tocilizumab	Standard care alone or with tocilizimab	28 days
Navarro-Millán I [13]	2020	Retrospective	Ward	Respiratory failure (non-intubated) and hyperinflammation	Not reported	11	3	Subcutaneous, 100 mg/6 h; frequency gradually decreased	Methylprednisolone, empiric antibiotics and hydroxychloroquine	Standard care	Hospital stay

TABLE 1. Continued.

First author	Year	Study design	Setting	Inclusion criteria	Mean baseline PaO_2/FiO_2	Anakinra patients	Control patients	Anakinra dosage	Concomitant treatments	Comparator	Follow-up
Pontali E [14]	2021	Retrospective	Ward and ICU	Respiratory failure (intubated and non-intubated) and hyperinflammation	262 (108.23)	63	44	Subcutaneous 100/8 h for 3 days, with tapering	Antibiotics, hydroxychloroquine, remdesivir, dexamethasone, thromboembolic prophylaxis	Standard care	Hospital stay
REMAP-CAP trial [32] (preprint)	2021	RCT	ICU	Patients receiving respiratory or cardiovascular support	106 (32.62)	373	1834	Intravenously as 300mg loading dose, followed by 100mg/6 h for 14 days	Steroids, remdesivir	Standard care alone or with tocilizumab or sarilumab	21 days
Zantah M [33] (preprint)	2021	Retrospective	Ward	Pneumonia	Not reported	51	33	Subcutaneous, 100 mg/6 h	Steroids if on oxygen	Tocilizumab	14 days

Abbreviations: PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; IL-6: interleukin 6; RCT: randomized clinical trial.

4. Discussion

This is the first meta-analysis that investigated the effect of the inhibition of IL-1 by anakinra on mortality and need for intubation in COVID-19 patients by evaluating both randomized controlled studies and non-randomized cohort studies [19, 47]. Overall, treatment with anakinra did not increase the incidence of superinfection, thromboembolic events and elevated serum transaminases and was associated with significant reductions in mortality. The benefit of anakinra treatment was more evident in less severe patients (baseline PaO_2/FiO_2 >200 or managed in a general ward) with hyper-inflammation. Even in the aftermath of global SARS-CoV-2 vaccination campaigns, these findings retain utmost importance since safe and effective treatments to inhibit inflammation and reduce mortality continue to be needed for the substantial proportion of unvaccinated individuals at risk of developing severe COVID-19 and for those without recent vaccination booster.

The rationale for IL-1 inhibition emerged during the first pandemic wave, with the understanding that patients with severe COVID-19 often develop a maladaptive, hyper-inflammatory response to the virus, characterized by deregulated release of pro-inflammatory mediators and originally termed 'cytokine storm' [2, 48, 49]. In these patients, extensive death of pneumocytes induced by viral replication results in the abundant release of intracellular pro-inflammatory mediators and danger signals, notably including IL-1α [10]. Once in the extracellular space, these mediators are sensed by immune cells (*e.g.*, resident alveolar macrophages, infiltrating lymphocytes or neutrophils), which are prompted to produce more cytokines, resulting in unrestrained activation of inflammatory cascades. Pivotal cytokines involved in this detrimental process include IL-1β, IL-6, IL-18, interferon-γ (IFNγ) and tumor necrosis factor (TNF) [50, 51]. Of note, not all patients with severe COVID-19 experience a bona fide cytokine storm with elevated circulating levels of these cytokines [52]; however, even in those patients without a 'classic' cytokine storm syndrome, some degree of hyper-inflammatory compartmentalization is observed in the lungs, which might benefit from cytokine-blocking or immunosuppressive therapies [53].

Anakinra is the first-in-class IL-1 inhibitor. It is a recombinant replica of the endogenous IL-1 receptor antagonist (IL-1Ra), which inhibits the receptor that transduce the pro-inflammatory activity of IL-1α and IL-1β. Anakinra is approved for the treatment of rheumatoid arthritis and Still's disease [54], but it is used off-label to treat a variety of conditions characterized by excess inflammation, including critical disease states [55, 56]. Notable therapeutic applications sharing pathogenic similarities with COVID-19 and hyper-inflammation include macrophage activation syndrome [58–60], and cytokine release syndromes triggered by infections in patients with autoimmune conditions [60, 61]. Of note, re-analysis of data from a large phase 3 randomized controlled trial of anakinra in sepsis and septic shock revealed a marked survival benefit, which was nevertheless restricted to patients with hyper-inflammation [11]. Equally important for use in the critical care setting, anakinra has an excellent safety profile and a half-life of only three hours, which ensures quick plasmatic clearance [62].

The findings of this study inform two critical aspects of treating COVID-19 with anakinra. First, patient selection is clearly critical. Based on presently available information, the severity of the individual's inflammatory response is the main criteria for eligibility to anakinra treatment. This meta-analysis indicates that the survival benefit is more marked in patients with hyper-inflammation. Although the definition of hyper-inflammation is not universal and varies slightly between studies, CRP serum concentrations, which largely reflect induction of acute phase reactants by IL-6 in liver cells, likely represent the most simple and pragmatic biomarker to evaluate the severity of ongoing inflammation, with high levels indicating a window of opportunity for IL-1 inhibition with anakinra. In fact, IL-1 induces the release of IL-6 and other different inflammatory mediators and established signaling mechanisms [63]. Indeed, a previous meta-analysis proved that the benefit of anakinra is maximum in COVID-19 patients with serum CRP concentrations above 50 mg/L [47]. Increased plasma levels of soluble urokinase plasminogen activator receptor (suPAR, $\geq$6 ng/mL), a proxy for calprotectin (S100A8/A9) and IL-1α bioactivity, were found to predate increases in other inflammatory biomarkers including CRP, IL-6, ferritin and D-dimers [64, 65], and to predict deterioration to respiratory failure in patients with COVID-19 pneumonia. Early screening of COVID-19 patients with suPAR was used to instruct treatment with anakinra in the SAVE-MORE RCT, which led to clear reductions in mortality rates compared to the standard-of-care [20]. Since suPAR is an optimal biomarker but not one that is universally available, a Polymerase Chain Reaction (CRP) >100 mg/dL appears as a logical and pragmatic screening option to identify candidates to IL-1 inhibition. Second, the timing of treatment administration is also critical. Anakinra is most effective when administered as early as pragmatically possible in patients with moderate-to-severe COVID-19. Conversely, anakinra treatment did not appear to result in a significant survival benefit for patients already receiving mechanical ventilation at the time of initiation. Although this observation is likely hindered by a small number of patients included in this subgroup decreasing statistical power, there is a clear possibility of anakinra being ineffective when administered too late during the disease, particularly when extensive organ damage results in the need for mechanical ventilation or ICU-level care.

Differences in patient selection and timing of administration likely explain the divergent outcomes observed in the two RCTs evaluating anakinra in COVID-19 completed so far, the CORIMUNO and SAVE-MORE trials. Specifically, the CORIMUNO trial enrolled patients with relatively mild disease (requiring maximum 3 L/min of supplemental oxygen), and with a relatively low threshold value for CRP (>25 mg/L), which together indicate that many patients had not developed hyperinflammation and thereby were not ideal candidates for anakinra treatment [21, 66]. Indeed, this study did not replicate the protective results observed with anakinra in observational investigations and was stopped because of assumed futility (even still, the 14-day mortality rate was 15% in anakinra patients and 24% in the standard care group) [21, 66]. Conversely, the SAVE-MORE trial enrolled patients based on

Study or Subgroup	Anakinra Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Aomar-Millan IF	0	10	14	133	0.7%	0.42 [0.03, 6.58]
Balkhair A	13	45	11	24	4.9%	0.63 [0.34, 1.19]
Bozzi G	9	65	19	55	4.5%	0.40 [0.20, 0.81]
Cauchois R	0	12	1	10	0.5%	0.28 [0.01, 6.25]
Cavalli G	9	62	98	330	5.0%	0.49 [0.26, 0.91]
CORIMUNO-ANA-1 trial	16	59	15	57	5.1%	1.03 [0.56, 1.88]
Dalekos GN	10	213	36	213	4.7%	0.28 [0.14, 0.55]
Declercq J	21	112	34	230	5.7%	1.27 [0.77, 2.08]
de la Calle C	11	20	9	20	5.0%	1.22 [0.65, 2.29]
ESCAPE	20	60	14	42	5.4%	1.00 [0.57, 1.75]
Franzetti M	19	56	30	56	6.0%	0.63 [0.41, 0.98]
Garcia-Garcia JA	22	125	36	270	5.8%	1.32 [0.81, 2.15]
Huet T	7	52	22	44	4.3%	0.27 [0.13, 0.57]
Iglesias-Julian E	1	9	2	18	1.0%	1.00 [0.10, 9.61]
Kharazmi AB	5	15	7	15	3.6%	0.71 [0.29, 1.75]
Kooistra EJ	4	21	7	39	2.9%	1.06 [0.35, 3.21]
Kyriazopoulou E	22	130	40	130	5.9%	0.55 [0.35, 0.87]
Langer-Gould A	9	41	24	52	4.9%	0.48 [0.25, 0.91]
Monti G	4	15	17	46	3.5%	0.72 [0.29, 1.81]
Navarro-Millan	1	11	0	3	0.6%	1.00 [0.05, 19.96]
Pontali E	9	63	28	65	4.8%	0.33 [0.17, 0.65]
REMAP-CAP	148	373	625	1834	7.4%	1.16 [1.01, 1.34]
SAVE-MORE	13	405	13	189	4.3%	0.47 [0.22, 0.99]
Zantah M	11	51	5	33	3.4%	1.42 [0.54, 3.73]
Total (95% CI)		**2025**		**3908**	**100.0%**	**0.69 [0.54, 0.87]**
Total events	384		1107			

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 76.36$, df = 23 ($P < 0.00001$); $I^2 = 70\%$
Test for overall effect: Z = 3.08 (P = 0.002)

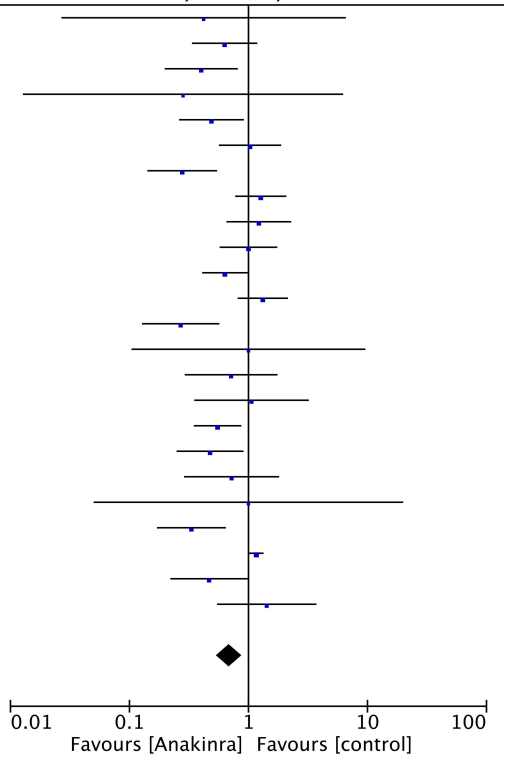

FIGURE 2. Forest plot for mortality. CI: confidence interval.

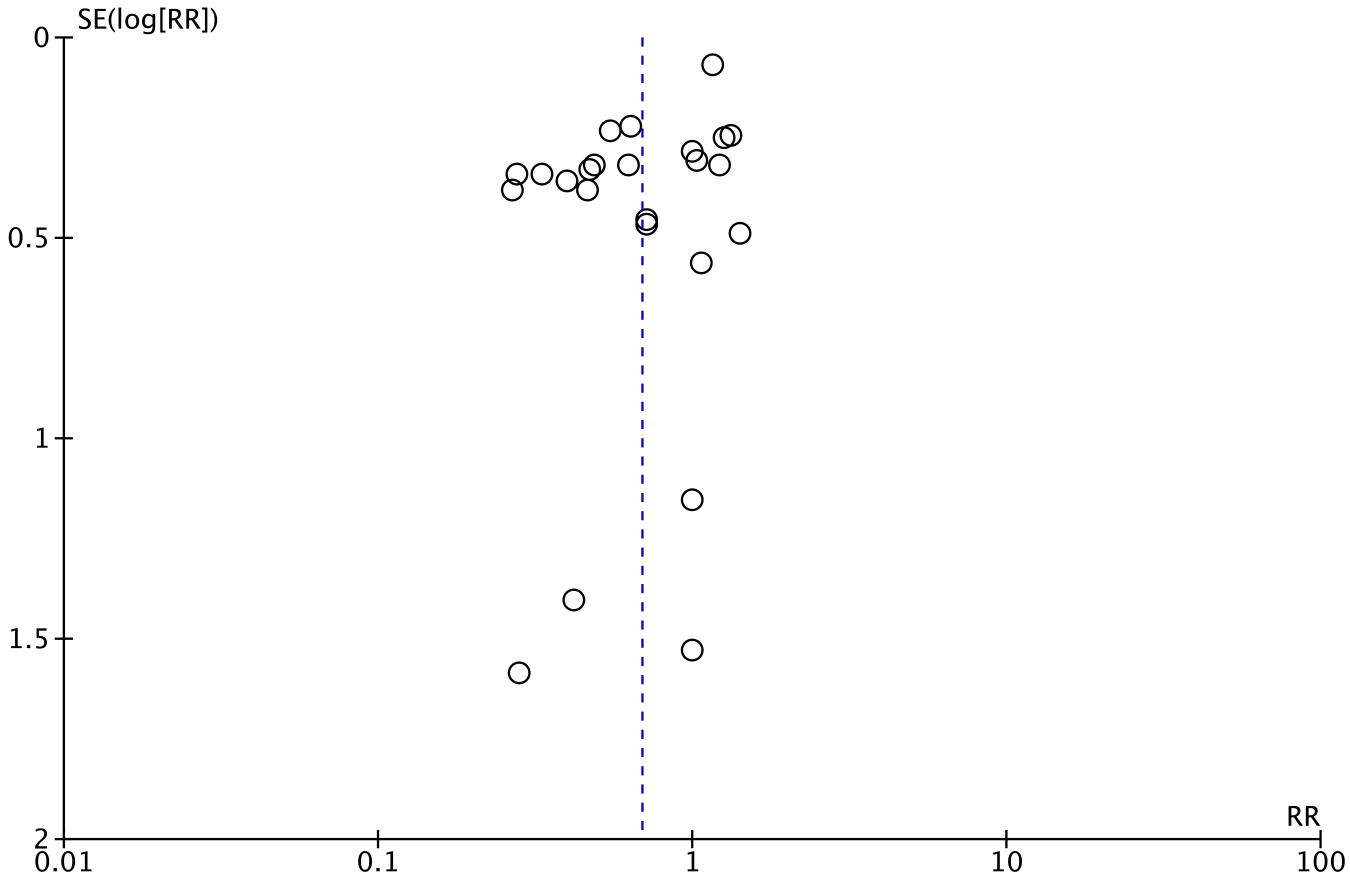

FIGURE 3. Funnel plot for mortality. RR: relative risk.

TABLE 2. Outcomes.

Outcome	Number of included studies	Anakinra patients	Control patients	RR	95% CI	P for effect	I^2 (%)
Overall studies	24	2025	3908				
Mortality*	24	384/2025 (19%)	1107/3908 (28%)	0.69	0.54 to 0.87	<0.001	70
Studies performed in ICU	4	161/424 (38%)	656/1934 (34%)	1.14	0.99 to 1.30	0.06	0
Studies performed in general ward	14	146/1296 (11%)	327/1684 (19%)	0.66	0.47 to 0.93	0.02	61
Studies with hyperinflammation as inclusion criteria	16	150/1131 (13%)	355/1609 (22%)	0.70	0.54 to 0.90	0.006	45
Studies without hyperinflammation as inclusion criteria	8	234/894 (26%)	752/2299 (33%)	0.68	0.44 to 1.05	0.08	82
Studies including patients with baseline $PaO_2/FiO_2 \leq 200$	9	246/761 (32%)	751/2318 (32%)	0.90	0.69 to 1.17	0.43	55
Studies including patients with baseline $PaO_2/FiO_2 > 200$	4	54/811 (7%)	117/597 (20%)	0.68	0.50 to 0.93	<0.001	11
Sensitivity Analysis							
Removing one study at time	All 95% CIs of RR <1 and $p < 0.05$						
Including only randomized clinical trials	5	202/974 (21%)	694/2335 (30%)	1.00	0.75 to 1.34	1.00	41
Need for invasive MV*	12	201/1242 (16%)	606/1856 (33%)	0.57	0.41 to 0.79	<0.001	66
Superinfection	15	168/1165 (14%)	188/1012 (19%)	0.94	0.58 to 1.54	0.81	65
Thromboembolic events	10	36/881 (4%)	28/779 (4%)	1.23	0.78 to 1.94	0.38	6
Elevated serum transaminases	8	214/738 (29%)	152/498 (31%)	1.07	0.75 to 1.54	0.71	58

Abbreviations: RR: risk ratio; CI: confidence interval; P: p-value; MV: mechanical ventilation; PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen; ICU: intensive care unit.
**Additional data sent by Dr. Navarro-Millán.*

biomarker profiling, using suPAR as a proxy for inflammation and IL-1 bioactivity, selected patients at high risk for clinical deterioration and disease severity, and administered anakinra early during the disease course. This study compared 28-day outcomes of patients receiving anakinra or placebo in addition to usual care (including dexamethasone) and confirmed a protective effect of anakinra treatment for COVID-19 [47].

Limitations of our meta-analysis include the retrospective observational design of the majority of included investigations, which implies concerns about the effect of potential biases and confounders; also of note, several included studies were conducted during the early phases of the global pandemic, when dexamethasone was not yet incorporated into the standard-of-care, and when makeshift management strategies for a previously unknown condition accounted for a higher global mortality. Moreover, the definition of hyperinflammation differs between the included. This issue is still a challenge for clinicians in daily practice and might causes a bias in the efficacy of anakinra.

5. Conclusions

In summary, this meta-analysis evaluating the impact of anakinra treatment in patients admitted to hospital with COVID-19 indicates significant reductions in mortality in less severe patients with hyper-inflammation; conversely, anakinra treatment appeared ineffective or marginally detrimental in patients requiring ICU-level care. Based on the results of the observational studies analyzed here, as well as the pivotal SAVE-MORE investigation, anakinra was approved by the European Medical Agency for use in adult patients with COVID-19 [67].

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article (and supplementary material).

AUTHOR CONTRIBUTIONS

GC, PN, GL, AGY, VVL, AZ, LD, GM and LP—designed the research study. AGY and VVL—performed the research. LP and PN—analyzed the data. GC, GL, GM, LD, LP and AZ—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

Prof. Dagna received consultation honoraria from SOBI (outside the current work). Prof Landoni and Prof Cavalli received speaker fees from SOBI (outside the current work). The other authors declare that they have no conflict of interest. Giovanni Landoni and Laura Pasin are serving as the Editorial Board members of this journal. We declare that Giovanni Landoni and Laura Pasin had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to OK.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1646393578981605376/attachment/Supplementary%20material.docx.

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