Anakinra in hospitalized non-intubated patients with coronavirus disease 2019: a systematic review and meta-analysis

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Abstract

Background: Acute respiratory distress syndrome and cytokine release syndrome are the major complications of coronavirus disease 2019 (COVID-19) associated with increased mortality risk.

Objectives: We performed a meta-analysis to assess the efficacy and safety of anakinra in adult hospitalized non-intubated patients with COVID-19.

Search methods: Relevant trials were identified by searching literature until 24 April 2021 using the following terms: anakinra, interleukin 1, coronavirus, COVID-19, SARS-CoV-2.

Selection criteria: Trials evaluating the effect of anakinra on the need for invasive mechanical ventilation and mortality in hospitalized non-intubated patients with COVID-19.

Results: Nine studies (n=1,119) were eligible for inclusion in the present meta-analysis. Their bias risk with reference to the assessed parameters was high. In pooled analyses, anakinra reduced the need for invasive mechanical ventilation (odds ratio, OR: 0·38, 95% confidence interval, CI: 0·17-0·85, p=0.02, I^2=67%; 6 studies, n=587) and mortality risk (OR: 0·32, 95% CI: 0·23-0·45, p <0·00001, I^2=0%; 9 studies, n=1,119) compared with standard of care therapy. There were no differences regarding the risk of adverse events, including liver dysfunction (OR: 0·75, 95% CI: 0·48-1·16, p>0·05, I^2=28%; 5 studies, n=591) and bacteremia (OR: 1·07, 95% CI: 0·42-2·73, p>0·05, I^2=71%; 6 studies, n=727).

Conclusions: Available evidence shows that treatment with anakinra reduces both the need for invasive mechanical ventilation and mortality risk of hospitalized non-intubated patients with COVID-19 without increasing the risk of adverse events. Confirmation of efficacy and safety requires randomized placebo-controlled trials.

Keywords: anakinra, interleukin 1, coronavirus, COVID-19, SARS-CoV-2

Key messages

- Our meta-analysis assessed the efficacy and safety of anakinra in hospitalized non-intubated patients with COVID-19.
- Anakinra reduced the need for invasive mechanical ventilation and mortality risk in non-intubated patients with COVID-19.
- Anakinra did not increase the liver enzymes or bacteremia risk in severely ill COVID-19 patients.

Introduction

At the end of 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of a cluster of pneumonia cases in Wuhan, in the Hubei Province of China and finally declared as pandemic in February 2020.[1] Until April 2021, about 147 million cases of coronavirus disease 2019 (COVID-19) and approximately 3 million deaths have been reported worldwide.[1] Although the majority of SARS-CoV-2 infections are mild to moderate, a considerable proportion of the infected patients develop severe disease and is hospitalized due to increased needs for ventilation.[1, 2] Among those, almost 30% are finally admitted to intensive care units (ICUs) to receive ventilation assistance because of acute respiratory distress syndrome (ARDS).[3-5] The reported mortality rates in such patients are high and range from 28 to 78%.[4, 6-8] Apart from dexamethasone in critically ill patients with COVID-19, there are no well-established effective therapies to treat SARS-CoV-2 infection.[9-11] Considering the noticed shortage of ICU beds and consequently the increased burden in medical wards,[12] identifying therapeutic modalities to improve adverse outcomes and prevent ICU admission and death in this population remains a public health emergency.

A subgroup of SARS-CoV-2 infected patients manifest hyperinflammatory symptoms that resemble the cytokine storm syndromes characterized by increased release of chemokines, growth factors and cytokines, including interleukins (ILs).[3, 13, 14] In this context, anakinra, an IL-1 receptor antagonist, used for the treatment of autoinflammatory disorders, has been considered in such patients.[15-17] Previous reports have demonstrated beneficial effects with anakinra in severe sepsis with multiorgan inflammatory dysfunction or secondary hemophagocytic lymphohistiocytosis,[18, 19] whereas case series and 2 recently published open label trials have

shown that treatment with anakinra is associated with laboratory and clinical improvement in COVID-19 patients with hyperinflammation.[20-26]

Considering the ongoing need for efficacious treatment modalities for patients severe COVID-19, we meta-analyzed available data reporting on the efficacy and safety of anakinra use in hospitalized non-intubated patients with COVID-19.

Materials and Methods

The present meta-analysis has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary).[27] Neither ethics approval nor patients' consent was required for this analysis.

Eligibility Criteria

Types of Studies

We aimed to include published randomized placebo-controlled trials (RCTs) in the present meta-analysis. In case of any lack of published RCTs, retrospective or prospective observational studies were included.

Study Participants

Studies including adult hospitalized non-intubated patients with COVID-19 were considered eligible. COVID-19 was diagnosed by quantitative RT-PCR and lung infiltrates depicted by either

chest x-ray or computerized tomography (CT). The definition of COVID-19 severity was based on the presence of respiratory failure and need for non-invasive ventilation.[11] In case of studies enrolling patients who required invasive mechanical ventilation, we included only those reporting separate data on their non-intubated subjects.

Interventions

Studies comparing anakinra with standard of care therapy in COVID-19 were included in the present meta-analysis. Standard of care therapy included anticoagulant treatment, azithromycin, hydroxychloroquine, antibiotics, or corticosteroids. Trials comparing anakinra with other immunomodulating drugs were excluded from the present meta-analysis.

Outcomes

Mortality and need for admission to the ICU with invasive mechanical ventilation were our primary outcomes of interest. The following adverse events were the secondary outcomes of interest: liver enzyme increase and bacteremia.

Information Sources

Relevant trials were identified by searching MEDLINE, EMBASE, CENTRAL and clinicaltrials.gov.gr until 24 April 2021 using the following terms: anakinra, interleukin 1, coronavirus, COVID-19, SARS-CoV-2. The trials included in our analysis were also scrutinized for other trials fulfilling our eligibility criteria.

Data Collection and Analysis

Selection of Studies

At the initial stage of review and each update, two authors (FB, SFN) independently selected the trials which were eligible for inclusion in the present meta-analysis.

Data Extraction and Management

Two review authors (FB and SFN) independently extracted data using an extraction form recording publication details, study population, randomization, allocation concealment, blinding, interventions and results of each trial. A standardized extraction tool was developed by consensus and refined after preliminary testing on a subset of the full-text articles. The extraction tool included a full description of study characteristics, the medications patients received (dose, frequency, route, duration) and the inferences made in each study. Any differences between them were resolved by consulting the other review authors (AL, EG, MK, EL, HM).

Assessment of Risk of Bias in Included Studies

In case of RCTs, we would assess the bias risk (low, unclear or high) of the following parameters: (i) sequence generation, (ii) allocation concealment, (iii) blinding (of participants, personnel and outcome assessors), (iv) incomplete outcome data addressed, (v) free of selective outcome reporting and vi) free of other bias.[28] Cohort studies were assessed using the Newcastle-Ottawa Scale.[29] The comparability domain of the Newcastle-Ottawa Scale was the primary differentiation point for a study's risk of bias in this context and was used to determine global risk

of bias (0 = high risk, 1 = some concerns, and 2 = low risk).[30] Any differences between FB and SFN were resolved by consultation.

Measurements of Treatment Effect

The odds ratio (OR) and the corresponding 95% confidence intervals (CIs) have been estimated in order to assess the treatment effect of anakinra on the investigated outcomes of interest.

Synthesis of Results

Missing Data

Trials not reporting on our primary outcomes of interest in the investigated population have not been included in the present work.

Assessment of Heterogeneity

Heterogeneity between trial results was tested using a standard chi-square test ($p < 0{\cdot}1$ was considered statistically significant) and I^2 statistic was used as a measure of heterogeneity.[9] The following ranges and descriptions were used: (i) 0–40%: might not be important, (ii) 30–60%: may represent moderate heterogeneity, (iii) 50–90%: may represent substantial heterogeneity and iv) 75–100%: considerable heterogeneity.

Subgroup Analysis and Investigation of Heterogeneity

In case of observed statistically significant heterogeneity, a random-effect meta-analysis was performed. Otherwise, a fixed-effect model was used.

Results

Study selection

Hitherto no placebo controlled RCT fulfilling our eligibility criteria has been completed yet (Figure 1). Of the 449 references identified by electronic and manual search, 9 studies were included in the present meta-analysis (n=1,119): 1 prospective and 6 retrospective cohorts, an open-label, bayesian randomized clinical trial (CORIMUNO-ANA-1) nested with a cohort and an open label trial (SAVE) with propensity-matched comparators.[25, 26, 31-37]

Study characteristics

The design of the studies along with the baseline characteristics of their subjects are demonstrated in Table 1. Anakinra was administered subcutaneously in most studies, but its dose and treatment duration varied across the included studies. Notably, 6 studies involved patients with severe COVID-19, but only those presenting with increased inflammation markers (C-reactive protein, CRP or ferritin). A high proportion of the study participants were diagnosed with comorbidities associated with increased mortality risk in COVID-19. Standard of care therapy included broad-spectrum antibiotics, azithromycin and hydroxychloroquine, whereas corticosteroid administration rates were high in 3 studies.

Bias Risk within Studies

As shown in Table 1, the noticed bias risk in most studies was high, mainly regarding their comparability and outcomes.

Effects of Interventions

The investigated outcomes of interest are presented in Table 2. The pooled analyses demonstrated that anakinra reduced the need for invasive mechanical ventilation (OR: 0·38, 95% CI: 0·17-0·85, p=0·02, I^2=67%; Figure 2A) and mortality risk (OR: 0·32, 95% CI: 0·23-0·45, p <0·00001, I^2=0%; Figure 2B) when compared with standard of care therapy.

No difference was noted regarding the risk of adverse events, including liver dysfunction (OR: 0·75, 95% CI: 0·48-1·16, p>0·05, I^2=28%; Figure 3A) and bacteremia (OR: 1·07, 95% CI: 0·42-2·73, p>0·05, I^2=71; Figure 3B).

Apart from mortality risk, moderate to substantial heterogeneity was noticed in the rest pooled analyses (Table 2).

Discussion

The present meta-analysis shows that anakinra reduces the need for invasive mechanical ventilation and lowers mortality risk in hospitalized non-intubated patients with COVID-19, without increasing the risk of adverse events.

The pandemic COVID-19 remains a public health emergency.[1] Although the majority of SARS-CoV-2 infections are mild to moderate, 14% of patients develop severe disease presenting

with dyspnea, hypoxia, or >50% lung involvement on imaging within 24 to 48 hours and 5% critical disease presenting with respiratory failure, shock and multi-organ dysfunction.[1, 2] One out of 3 hospitalized patients with COVID-19 develop ARDS and are finally admitted to ICUs to receive ventilation assistance with high mortality rates.[3-8] No well-established effective therapies confronting COVID-19 have been found yet.[9] Only dexamethasone has been shown to significantly reduce 28-day mortality in patients with critical COVID-19.[10, 11] Remdesivir, a novel nucleotide analogue, has been proposed in hospitalized patients with severe COVID-19 requiring low-flow supplemental oxygen, given the potential reduction in time to clinical improvement,[10, 11, 38-40] but the World Health Organization recommends against its routine use.[11] In areas with high COVID-19 prevalence, the high number of severely ill patients with COVID-19 and ARDS exceeds the maximum capacity of ICUs.[12] Due to the shortage of ICU beds, many SARS-CoV-2 infected patients with ARDS have received maximum supportive treatment with non-invasive ventilation in medical wards, while they are awaiting for ICU access and further therapeutic approaches.[12] Although an effective vaccination remains the cornerstone to combat the emerging pandemic COVID-19,[41] finding therapies to reduce mortality and prevent ICU admission in this population remains an imperative need.

A few SARS-CoV-2 infected patients develop symptoms indicating severe inflammation that is alike to other cytokine storm syndromes, such as secondary hemophagocytic lymphohistiocytosis, macrophage activation syndrome and chimeric antigen receptor [CAR] T-cell-mediated cytokine release syndrome.[3, 13, 14, 42] This hyper-inflammation is mirrored systemically by pronounced increases in CRP and ferritin levels and its orchestrating mediators include various cytokines and chemokines, such as IL-6, IL-1, IL-10, granulocyte-colony stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and

tumor necrosis factor (TNF)-α.[3, 13, 14, 42] Hence, various monoclonal antibodies against different cytokines or JAK–STAT inhibitors represent attractive therapeutic options in this setting.[13, 17, 42] Indeed, anakinra, which blocks the activity of the proinflammatory cytokines IL-1α and IL-1β and has been previously approved for the treatment of autoinflammatory disorders, such as adult-onset Still's disease, systemic-onset juvenile, idiopathic arthritis, and familial Mediterranean fever, has been considered in such cases.[15, 32] Moreover, its remarkable safety profile and short half-life makes anakinra more appealing to use in severely ill patients.[15] Indeed, previous reports have confirmed its efficacy on cytokine release syndromes related with multiorgan inflammatory dysfunction in severe sepsis or secondary hemophagocytic lymphohistiocytosis.[18, 19]

Although no placebo-controlled RCTs have been completed yet, accumulating evidence favors the use of anakinra for the treatment of COVID-19. Case series and 2 recently published open label trials have shown that anakinra is associated with laboratory and clinical improvement in COVID-19 patients with hyperinflammation.[20-26] Previous meta-analyses ($n \leq 184$) including up to 4 observational studies demonstrated that anakinra was associated with a lower mortality risk and need for invasive mechanical ventilation compared with standard of care therapy.[43-45] In contrast, the present meta-analysis integrates data from 9 studies (n=1,119) and focuses on the efficacy and safety of anakinra in hospitalized non-intubated patients with COVID-19.

Considering the reduction in both the need for invasive mechanical ventilation and mortality risk, our meta-analysis is the most updated and largest to propose that anakinra represents an effective treatment for non-intubated patients with COVID-19. Of note, most studies in our meta-analysis enrolled patients with hyperinflammation. In line with our findings, RCTs (RECOVERY and REMAP-CAP) handling tocilizumab, an IL-6 inhibitor, demonstrated the

efficacy of active treatment in hospitalized COVID-19 patients with increased inflammatory markers.[46, 47]

A recent report denoted that anakinra and tocilizumab may increase the risk for blood stream infections in ICU patients (n=235) with severe COVID-19 (HR: 3·20, 95% CI: 1·31-7·81, p=0·011).[48] Despite the difficulty in defining the side effects of a treatment modality in critically ill patients with systemic disease receiving additional therapies, our results derived from a larger sample indicate that anakinra remains a safe therapeutic option in SARS-CoV-2 infected patients, since it was not associated with a high risk of bacteremia or liver dysfunction.

The acknowledged limitations of this meta-analysis relate with the design of the included studies, their sample size and follow-up disparities, along with the different dosage and route of anakinra administration.

Conclusions

Available evidence shows that treatment with anakinra reduces both the need for invasive mechanical ventilation and mortality risk in hospitalized non-intubated patients with COVID-19. In the context of the current pandemic and the great shortage of ICUs beds, treatment with anakinra should be promptly tested by randomized placebo-controlled trials.

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Contributorship: Dr Barkas, Dr Ntekouan and Dr Liontos contributed to the acquisition, analysis and interpretation of data for the present work and drafted the present manuscript. Dr Kosmidou, Prof Liberopoulos and Prof Milionis contributed to the conception and design of the present work and they revised it critically for important intellectual content. All authors finally approved the version to be published and agreed to be accountable for all aspects of the present work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement: The data underlying this article are available in the article.

References

1 WHO. Coronavirus Disease (COVID-19) Pandemic. Assessed from https://www.who.int/emergencies/diseases/novel-coronavirus-2019 on 11 May 2020. 2020.

2 Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239-42.

3 Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020.

4 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.

5 Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507-13.

6 Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8(5):475-81.

7 Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA 2020;323(16):1612-4.

8 Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020;323(16):1574-81.

9 Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA 2020.

10 Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med 2020.

11 Lamontagne F, Agoritsas T, Macdonald H, et al. A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379.

12 Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020;395(10231):1225-8.

13 Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033-4.

14 Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020.

15 Cavalli G, Dinarello CA. Treating rheumatological diseases and co-morbidities with interleukin-1 blocking therapies. Rheumatology (Oxford) 2015;54(12):2134-44.

16 Cavalli G, Colafrancesco S, Emmi G, et al. Interleukin 1alpha: a comprehensive review on the role of IL-1alpha in the pathogenesis and treatment of autoimmune and inflammatory diseases. Autoimmun Rev 2021;20(3):102763.

17 Alunno A, Najm A, Mariette X, et al. Immunomodulatory therapies for SARS-CoV-2 infection: a systematic literature review to inform EULAR points to consider. Ann Rheum Dis 2021.

18 Shakoory B, Carcillo JA, Chatham WW, 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. Crit Care Med 2016;44(2):275-81.

19 Eloseily EM, Weiser P, Crayne CB, et al. Benefit of Anakinra in Treating Pediatric Secondary Hemophagocytic Lymphohistiocytosis. Arthritis Rheumatol 2020;72(2):326-34.

20 Monteagudo LA, Boothby A, Gertner E. Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome. ACR Open Rheumatol 2020;2(5):276-82.

21 Pontali E, Volpi S, Antonucci G, et al. Safety and efficacy of early high-dose IV anakinra in severe COVID-19 lung disease. J Allergy Clin Immunol 2020;146(1):213-5.

22 Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. Ann Rheum Dis 2020;79(10):1381-2.

23 Clark KEN, Collas O, Lachmann H, Singh A, Buckley J, Bhagani S. Safety of intravenous anakinra in COVID-19 with evidence of hyperinflammation, a case series. Rheumatol Adv Pract 2020;4(2):rkaa040.

24 Navarro-Millan I, Sattui SE, Lakhanpal A, Zisa D, Siegel CH, Crow MK. Use of Anakinra to Prevent Mechanical Ventilation in Severe COVID-19: A Case Series. Arthritis Rheumatol 2020;72(12):1990-7.

25 Tharaux P-L, Pialoux G, Pavot A, et al. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. The Lancet Respiratory Medicine 2021;9(3):295-304.

26 Kyriazopoulou E, Panagopoulos P, Metallidis S, et al. An open label trial of anakinra to prevent respiratory failure in COVID-19. Elife 2021;10.

27 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62(10):1006-12.

28 Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

29 Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Assessed from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

30 Viswanathan M, Patnode CD, Berkman ND, et al. Recommendations for assessing the risk of bias in systematic reviews of health-care interventions. J Clin Epidemiol 2018;97:26-34.

31 Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. The Lancet Rheumatology 2020;2(7):e393-e400.

32 Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. The Lancet Rheumatology 2020;2(6):e325-e31.

33 Cauchois R, Koubi M, Delarbre D, et al. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. Proc Natl Acad Sci U S A 2020;117(32):18951-3.

34 Balkhair A, Al-Zakwani I, Al Busaidi M, et al. Anakinra in hospitalized patients with severe COVID-19 pneumonia requiring oxygen therapy: results of a prospective, open-label, interventional study. Int J Infect Dis 2020.

35 Bozzi G, Mangioni D, Minoia F, et al. Anakinra combined with methylprednisolone in patients with severe COVID-19 pneumonia and hyperinflammation: an observational cohort study. J Allergy Clin Immunol 2020.

36 Cavalli G, Larcher A, Tomelleri A, et al. Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. The Lancet Rheumatology 2021;3(4):e253-e61.

37 Franzetti M, Forastieri A, Borsa N, et al. IL-1 Receptor Antagonist Anakinra in the Treatment of COVID-19 Acute Respiratory Distress Syndrome: A Retrospective, Observational Study. J Immunol 2021;206(7):1569-75.

38 Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020;383(19):1813-26.

39 Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236):1569-78.

40 Rochwerg B, Agarwal A, Zeng L, et al. Remdesivir for severe covid-19: a clinical practice guideline. BMJ 2020;370:m2924.

41 Ong E, Wong MU, Huffman A, He Y. COVID-19 coronavirus vaccine design using reverse vaccinology and machine learning. bioRxiv 2020.

42 Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med 2020;383(23):2255-73.

43 Kim MS, An MH, Kim WJ, Hwang TH. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. PLoS Med 2020;17(12):e1003501.

44 Pasin L, Cavalli G, Navalesi P, et al. Anakinra for patients with COVID-19: a meta-analysis of non-randomized cohort studies. Eur J Intern Med 2021.

45 Putman M, Chock YPE, Tam H, et al. Antirheumatic Disease Therapies for the Treatment of COVID-19: A Systematic Review and Meta-Analysis. Arthritis Rheumatol 2021;73(1):36-47.

46 Investigators R-C, Gordon AC, Mouncey PR, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med 2021.

47 RECOVERY Collaborative Group, Horby P, Pessoa-Amorim G. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial.medRxiv. 2021;preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1. 2021.

48 Buetti N, Ruckly S, de Montmollin E, et al. COVID-19 increased the risk of ICU-acquired bloodstream infections: a case-cohort study from the multicentric OUTCOMEREA network. Intensive Care Med 2021;47(2):180-7.

Legends to Figures

Figure 1. PRISMA flowchart of study selection

Figure 2. Forest plot for (A) the need for invasive mechanical ventilation and (B) mortality risk

Figure 3. Forest plot for adverse effects: (A) liver enzyme increase and (B) bacteremia

Legends to Tables

Table 1. Characteristics of the included cohorts

* Mortality and need for IMV was included in the secondary outcomes of interest

Abbreviations: ARDS, acute respiratory distress syndrome; bid, 2 times a day; CRP, C-reactive protein; CT, computerized tomography; IMV, invasive mechanical ventilation; IL-6, interleukin-6; iv, intravenously; N/A, not applicable; PEEP, positive end-expiratory pressure; SARS-CoV-2, serious acute respiratory syndrome coronavirus 2; tid, 3 times a day, qd, once a day; qid, 4 times a day; sc, subcutaneously; WHO-CPS, WHO Clinical Progression Scale

Table 2. Outcomes of interest

Table 1

	Huet et al. [31]	**Cavalli et al. 2020 [32]**	**Cauchois et al. [33]**	**Balkhair et al. [34]**
Type of study	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective open label trial
Bias risk	High	High	High	High
Anakinra (dose, route, duration)	100 mg (sc) bid for 3 days, followed by 100 mg qd for 7 days	100 mg (sc) bid or 10 mg/kg (iv) (divided in two doses) until sustained clinical benefit (>75% CRP reduction and pO_2/FiO_2 >200 mmHg) or adverse events (death, bacteremia or side effects)	300 mg (iv) qd for 5 days, followed by 200 mg qd for 2 days and 100 mg qd for 1 day	100 mg (sc) bid for 3 days, followed by 100 mg (sc) qd for ≤7 days
Control group	Standard of care	Standard of care	Standard of care	Standard of care
Primary Outcome	IMV need or survival in 7 days	IMV need or survival in 21 days	IMV need or survival in 20 days	IMV need or survival in 14 days

Inclusion criteria	-SARS-CoV-2 infection -Bilateral infiltrates on a lung CT scan or chest x-ray -$SpO_2 \leq 93\%$ under ≥ 6 L/min of O_2 or $SpO_2 \leq 93\%$ on 3 L/min with a saturation on ambient air decreasing by 3% in the previous 24 h	-SARS-CoV-2 infection -Bilateral infiltrates on lung CT scan or chest x-ray -pO_2/FiO_2 <200 mmHg with PEEP ≥ 5 cm H_2O -CRP >100 mg/L or/and ferritin >900 ng/ml	-SARS-CoV-2 infection -Pneumonia rapidly deteriorating -Increasing O_2 requirement of >4 L/min within the previous 12 h -CRP >110 mg/L	-SARS-COV-2 infection -Bilateral infiltrates on chest x-ray - respiratory rate >30/min and SpO_2 <90% on ambient air or SpO_2 <93% under O_2 >6L/min or ARDS
N of participants	96	52	22	69
Sex (male), %	64	82	55	75
Mean age, years	71	67	60	51
Comorbidities				
Smoking, %	N/A	11	18	N/A

Body mass index, kg/m^2	27.3	N/A	26.3	N/A
Hypertension, %	63	50	32	41
Diabetes, %	31	21	13	41
Coronary artery disease, %	20	11	13	N/A
Pulmonary diseases, %	20	8	26	N/A
Chronic kidney disease, %	N/A	11	5	N/A
Inflammatory markers				
Lymphocyte count cells/mm^3	990	N/A	N/A	1200
CRP, mg/L	164	164	155	145
D-dimers, ng/mL	3786	N/A	N/A	850

Lactate dehydrogenase, U/L	471	471	N/A	519
Ferritin, ng/mL	2025	1497	1481	1274
Interleukin-6, pg/mL	93	N/A	N/A	77
Concomitant therapies, %				
Hydroxychloroquine	38	100	100	7
Azithromycin	43	100	100	87
Broad-spectrum antibiotics	92	10	100	99
Corticosteroids	2	0	0	59
Duration of symptoms before treatment, days	7 days	N/A	N/A	9

	Bozzi et al. [35]	Cavali 2021 et al. [36]	Franzetti et al. [37]	CORIMUNO-ANA-1 [25]	Kyriazopoulou et al. [26]
Type of study	Retrospective cohort	Retrospective cohort	Retrospective cohort	Open-label, Bayesian randomized clinical trial (CORIMUNO-ANA-1), nested within the CORIMUNO-19 cohort	Open label trial (SAVE) with propensity-matched standard-of care comparators
Bias risk	High	High	High	Some	Some
Anakinra (dose, route, duration)	200 mg (sc) tid for 3 days, followed by 100	10 mg/kg (iv) (divided in two doses) until sustained clinical	100 mg (sc) qid or 200 mg (iv) tid for 7 days	200 mg (iv) bid on days 1–3, 100 mg bid on day 4, 100 mg qd on day 5	100 mg (sc) qd for 10 days

	mg (sc) tid up to day 14	benefit (sustained improvement of respiratory parameters and >75% CRP reduction)			
Control group	Standard of care	Standard of care	Standard of care	Standard of care	Standard of care
Primary Outcome	Survival in 28 days	Survival in 28 days	Survival in 28 days	IMV need or survival in 14 days	Severe respiratory failure incidence by day 14 *
Inclusion criteria	-SARS-CoV-2 infection -Pneumonia - Respiratory failure with need of supplemental	-SARS-CoV-2 infection - Bilateral lung infiltrates on a lung CT scan or chest x-ray	-SARS-CoV-2 infection - Bilateral lung infiltrates on a lung CT scan or chest x-ray	-SARS-CoV-2 infection -Need for ≥3 L/min of oxygen by mask or nasal cannula but	- SARS-CoV-2 infection - Lung infiltrates on a lung CT scan or chest x-ray compatible with

	O_2 (O_2 therapy from 40% FiO_2 venturi mask to MIV) -CRP >100 mg/L and/or ferritin ≥1000 ng/mL	-pO_2/FiO_2 <300 mmHg -CRP >100 mg/L or/and ferritin >900 ng/ml	-PO_2/FiO_2 <250 mmHg on ambient air requiring ventilatory support, either with CPAP or orotracheal intubation, to achieve a PEEP ≥8 cm H_2O - CRP ≥100 mg/L and/or ferritin ≥900 ng/ml	without ventilation assistance - WHO-CPS ≥5 -CRP ≥25 mg/L	lower-tract respiratory infection -suPAR ≥6 ng/ml
N of participants	120 (39 intubated subjects)	337	112 (12 intubated subjects)	116	260
Sex (male), %	80	75	78	66	63

Mean age, years	62	67	67	66	64
Comorbidities					
Smoking, %	N/A	N/A	N/A	17	N/A
Body mass index, kg/m^2	N/A	N/A	N/A	26.6	N/A
Hypertension, %	N/A	N/A	53	N/A	48
Diabetes, %	N/A	20	17	29	28
Coronary artery disease, %	N/A	N/A	18	N/A	9
Pulmonary diseases, %	N/A	N/A	7	15	7
Chronic kidney disease, %	N/A	N/A	N/A	7	2
Inflammatory markers					

Lymphocyte count, cells/mm^3	750	900	689	800	964
CRP, mg/L	152	130	175	121	58
D-dimers, ng/mL	1246	N/A	3096	1111	N/A
Lactate dehydrogenase, U/L	N/A	380	423	447	N/A
Ferritin, ng/mL	1555	1279	1620	1298	572
Interleukin-6, pg/mL	N/A	N/A	N/A	N/A	N/A
Concomitant therapies, %					
Hydroxychloroquine	98	100	100	5	48
Azithromycin	N/A	100	100	13	77
Broad-spectrum antibiotics	N/A	100	100	67	N/A
Corticosteroids	54	18	0	51	38

Duration of symptoms before treatment, days	7	N/A	7	10	8

Table 2

Outcome	Included studies (n)	Anakinra patients	Control patients	Odds Ratio	95% Confidence Interval	P for effect	I^2 (%)
Overall Studies	9	485	634				
Need for invasive mechanical ventilation	6	63/317 (20%)	114/270 (42%)	0.38	0.17-0.85	0.02	67
Mortality	9	64/485 (13%)	194/634 (31%)	0.32	0.23-0.45	<0.00001	0
Liver enzyme increase	5	57/322 (18%)	62/269 (23%)	0.75	0.48-1.16	0.20	28
Bacteremia	6	46/391 (12%)	48/336 (14%)	1.07	0.42-2.73	0.90	71

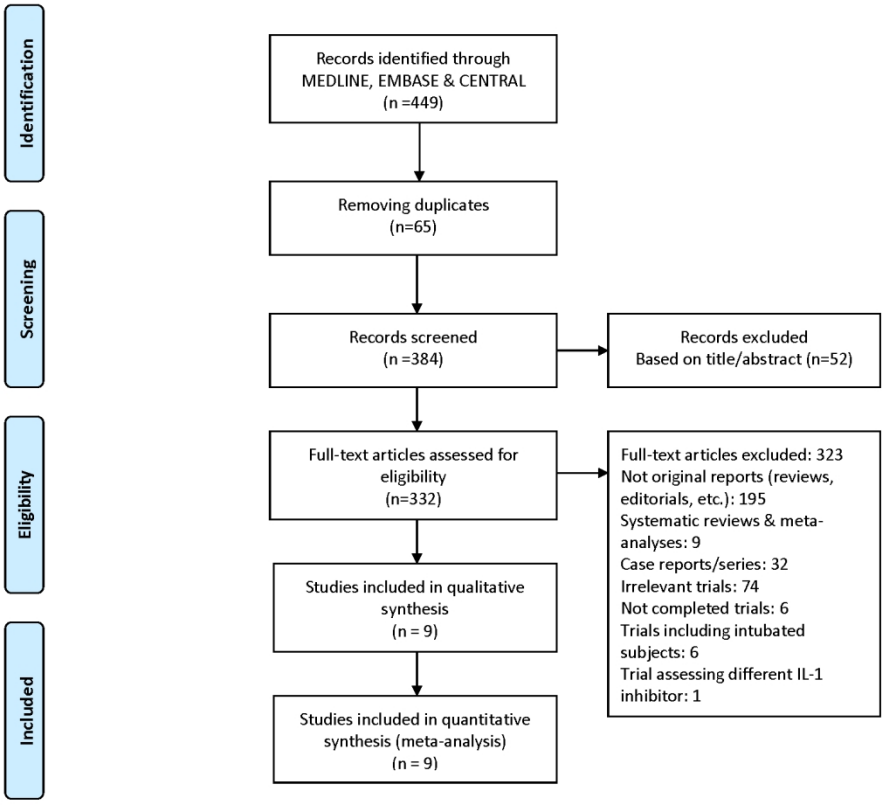

Figure 1

71x58mm (600 x 600 DPI)

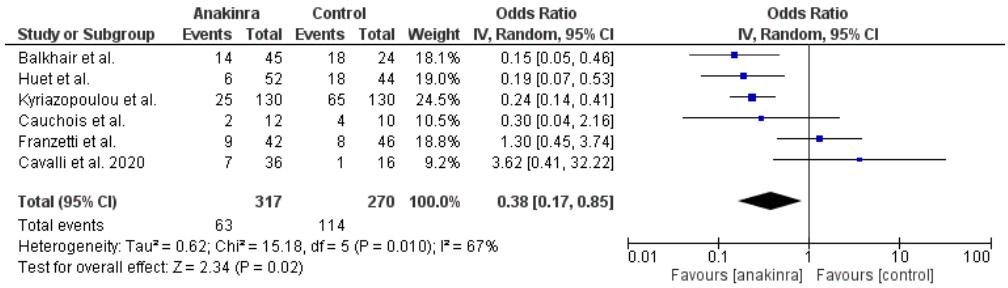

Figure 2a

32x9mm (600 x 600 DPI)

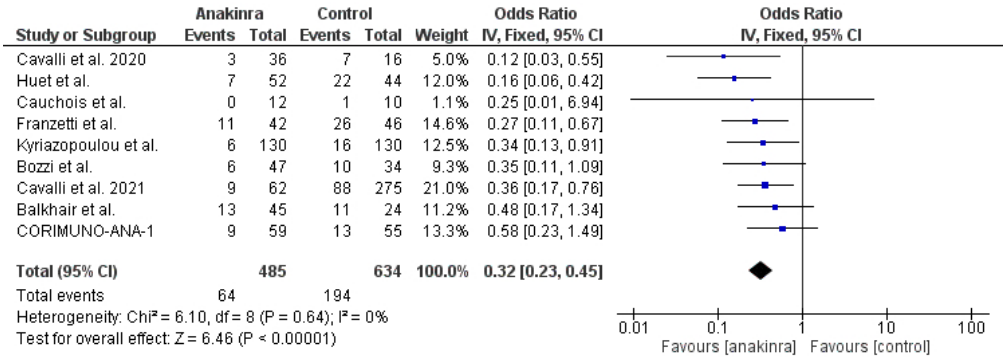

Figure 2b

31x11mm (600 x 600 DPI)

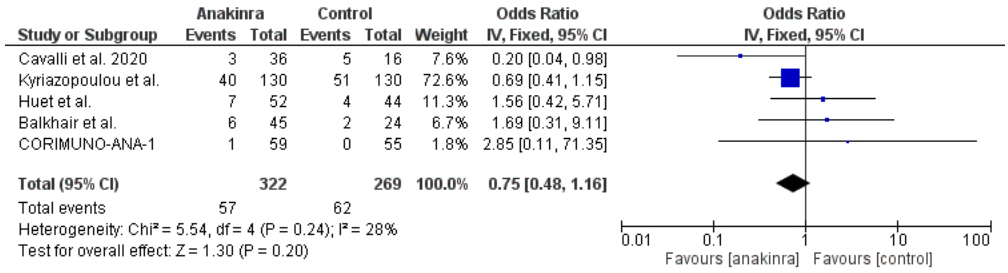

Figure 3a

31x8mm (600 x 600 DPI)

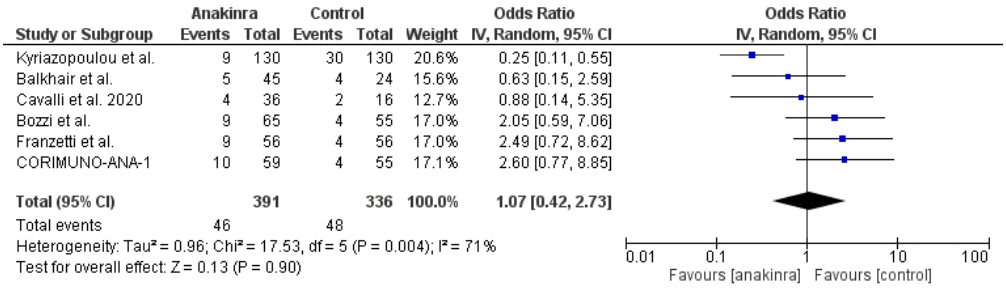

Figure 3b

32x9mm (600 x 600 DPI)