Efficacy and safety of granulocyte–macrophage colony-stimulating factor (GM-CSF) antibodies in COVID-19 patients: a meta-analysis

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Abstract
Objective This study aims to determine the efficacy and safety of granulocyte–macrophage colony-stimulating factor (GM-CSF) antibodies in COVID-19 patients.

Methods We searched Cochrane Library, PubMed, Embase, and ClinicalTrials.gov databases until July 27, 2022. Both randomized control trials (RCTs) and cohort studies were included and analyzed separately. The outcomes included mortality, incidence of invasive mechanical ventilation (IMV), ventilation improvement rate (need oxygen therapy to without oxygen therapy), secondary infection, and adverse events (AEs). The odds ratio (OR) with a 95% confidence interval (CI) was calculated by a random-effects meta-analysis model.

Results Five RCTs and 2 cohort studies with 1726 COVID-19 patients were recruited (n = 866 in the GM-CSF antibody group and n = 891 in the control group). GM-CSF antibodies treatment reduced the incidence of IMV, which was supported by two cohort studies (OR 0.16; 95% CI 0.03, 0.74) and three RCTs (OR 0.62; 95% CI 0.41, 0.94). GM-CSF antibodies resulted in slight but not significant reductions in mortality (based on two cohort studies and five RCTs) and ventilation improvement (based on one cohort study and two RCTs). The sensitive analysis further showed the results of mortality and ventilation improvement rate became statistically significant when one included study was removed. Besides, GM-CSF antibodies did not increase the risks of the second infection (based on one cohort study and five RCTs) and AEs (based on five RCTs).

Conclusion GM-CSF antibody treatments may be an efficacious and well-tolerant way for the treatment of COVID-19. Further clinical evidence is still warranted.

Keywords Meta-analysis · Granulocyte–macrophage colony-stimulating factor · Antibody · COVID-19

Introduction
The COVID-19 pandemic is still threatening public health with its serious outcomes and strong infectivity (Chen et al. 2021). By 30th August 2022, confirmed COVID-19 cases surpassed 601 million, and more than 6.48 million deaths have been reported worldwide. The most common symptoms of COVID-19 include fever, dry cough, shortness of breath, and severe complications include pneumonia and even acute respiratory distress syndrome (ARDS) (Wiersinga et al. 2020). Vaccinations still could not give immediate or 100% protection and may be resistant by a mutant virus. Thus, it is still urgent to develop and evaluate new therapeutic strategies for COVID-19.

Granulocyte–macrophage colony-stimulating factor (GM-CSF) is an important myelopoietic growth factor and pro-inflammatory cytokine which had been identified to play a key role in lung inflammatory and immunological...
diseases (Mehta et al. 2020). It had been reported that GM-CSF expression is increased in the leukocytes of patients with COVID-19 (Zhou et al. 2020). Because of its immune hyperactivity, GM-CSF may play a significant role in the pathogenesis of COVID-19. GM-CSF antibodies inhibiting the GM-CSF signaling axis by targeting GM-CSF, such as Gimsilumab, lenzilumab, namilumab, and otilimab, or GM-CSF receptors (GM-CSFR), such as mavrilimumab. Several clinical trials of GM-CSF antibodies for the treatment of COVID-19 have been conducted. Antagonizing the GM-CSF receptor or directly binding circulating GM-CSF may be beneficial for treating hyperinflammation-related lung injury (Bonaventura et al. 2020; Lang et al. 2020; Sterner et al. 2019). However, the efficacy and safety of GM-CSF antibodies in the treatment of COVID-19 have not been clarified (Khan et al. 2020; Rizk et al. 2020). Therefore, the present meta-analysis was conducted to investigate the effects of GM-CSF antibody treatment in COVID-19 patients.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Liberati et al. 2009) and registered in PROSPERO (CRD42020221450; https://www.crd.york.ac.uk/prospero/).

Inclusion and exclusion criteria and data collection

Inclusion criteria were: (1) studies concerning GM-CSF antibody treatment alone or in combination with other specific treatments for adult COVID-19 patients; (2) studies were designed as randomized control trials (RCTs) or cohort studies.

Exclusion criteria were: (1) studies without controls or only self-control; (2) data were not available or were repeated; (3) reviews, editorials, letters, commentaries.

Search strategy

The search strategy was conducted by A.X. and Y.L. for the Cochrane Library, Embase, PubMed, and ClinicalTrials.gov. References for each piece of literature were manually reviewed. Any disagreement was solved by ZX. In detail, relevant literature published from 1 December 2019 and until 27 July 2022 was searched with the strategies shown in Supplemental Tables 1.

Study selection and data extraction

Literature selection was undertaken by A.X. and Y.L. The duplicate literature was excluded using EndNote 20; the eligible literature with full text were reviewed and selected according to the inclusion and exclusion criteria. J.G. and W.W. gathered data from relevant literature, including therapeutic strategies, the number of recruited patients, ventilation conditions, death number, severe case number, ICU admission risk, risks of secondary infection, and severe events (e.g., sepsis, acute kidney injury, and cardiac injury).

Assessment of study quality

For cohort studies, the Newcastle–Ottawa Scale (NOS) (Wells et al. 2014) was used to assess study quality (Supplemental Table 2). For RCTs, Cochrane risk-of-bias tool was used (Supplemental Fig. 1).

Statistical analysis

Forest plots were used to display the pooled estimates, which were reported as odds ratios (ORs) and 95% confidence intervals (CIs). As the studies included in the analysis are not functionally identical (such as the use of different kinds of drugs and different standard of care methods), a random-effects model (Mantel–Haenszel method) was employed for the meta-analysis. Heterogeneity among studies was evaluated by \( \chi^2 \), \( I^2 \), \( df \), and \( Tau^2 \). \( I^2 \) values selected zero. \( I^2 \) values of 25%, 50%, and 75% were, respectively, indicated low, moderate, and high heterogeneity. Funnel plots and Egger’s asymmetry test were used to assess publication bias. Revman 5.3 was used for statistical processing. In addition, to evaluate the strength and stability of the meta-analysis, sensitivity analysis was conducted by omitting the individual studies one by one.

Results

Selection of eligible literatures

According to the Fig. 1, 1480 pieces of literatures were initially identified based on their titles and abstracts; 212 literatures were removed for duplicate; 1260 literatures were removed by the inclusion and exclusion criteria. Finally, the meta-analysis included seven pieces of relevant literatures (Cremer et al. 2021; Criner et al. 2022; De Luca et al. 2020; Fisher et al. 2022; Patel et al. 2022; Temesgen et al. 2020, 2021). Of note, one preprint of Temesgen et al. 2021 was included, because it is the results of a registered clinical trial from ClinicalTrials.gov (number: NCT04351152).

Characteristics of included literatures

The GM-CSF antibody group (\( n = 866 \)) and the control group (\( n = 891 \)) were from seven studies (Cremer et al.
Two of included studies were high-quality cohort studies (De Luca et al. 2020; Temesgen et al. 2020) and the other five were RCTs (Cremer et al. 2021; Criner et al. 2022; Fisher et al. 2022; Patel et al. 2022; Temesgen et al. 2020, 2021); two of included studies were used anti-GM-CSFR antibody (Cremer et al. 2021; De Luca et al. 2020), and the other five were used anti-GM-CSF antibodies (Criner et al. 2022; Fisher et al. 2022; Patel et al. 2022; Temesgen et al. 2020, 2021). Characteristics of the included studies are summarized in Table 1, including the study design (type of study), treatment methods, sample sizes, the standard of care, primary endpoints, and secondary endpoints. The NOS scores of included non-RCTs are shown in Supplementary Table 2 and the risk of bias of included RCTs was shown in Supplementary Fig. 1.
### Table 1  Characteristics of the studies included in the meta-analysis

| Reference       | Type of study                          | Dosage of GM-CSF antibodies | Control N | Method | Outcomes                                      | Standard care                                      |
|-----------------|----------------------------------------|-------------------------------|-----------|--------|-----------------------------------------------|---------------------------------------------------|
| Nonrandomized studies (cohort studies) |                                        |                               |           |        |                                               |                                                   |
| Luca et al. 2020 | Single-center prospective cohort study | Mavrilimumab iv 6 mg/kg and | 13        | Standard care | Clinical improvement endpoint | Oral hydroxychloroquine (200 mg twice a day), intravenous azithromycin (500 mg, once daily until patient tested negative for urine antigen for Legionella pneumophila), oral lopinavir–ritonavir (400 and 100 mg, respectively, twice a day), and respiratory support with supplemental oxygen or non-invasive ventilation with continuous positive airway pressure (with a positive end expiratory pressure of 10 cm of water) |
| Temesgen et al. 2020 | Single-center retrospective cohort study | lenzilumab 600 mg iv and | 12        | Standard care | Incidence of clinical improvement | Remdesivir and/or dexamethasone and US FDA guidelines |
| RCTs            |                                        |                               |           |        |                                               |                                                   |
| Patel et al. 2022 | Large, global, double-blind, randomized, placebo-controlled study | 90 mg infusion of otilimab and standard care | 397       | Standard care | The primary endpoint: Proportion of patients alive and free of respiratory failure; The secondary endpoints: time to recovery from respiratory failure; time to all-cause mortality; time to last dependence on supplementary oxygen; time to final ICU discharge; time to first discharge from investigator site; time to final hospital discharge | US FDA guidelines |
| Fisher et al. 2022 | Randomized, multi-arm, parallel-group, open-label, trial | Namilumab (150 mg) iv once and standard care | 55        | Standard care | The primary endpoint: CRP concentration; The secondary endpoints: WHO clinical progression scale | UK guidelines |
| Cremer et al. 2021 | Multicenter, double-blind, randomized trial | Mavrilimumab iv 6 mg/kg and standard care | 21        | Standard care | The primary endpoint: patients alive and off supplemental oxygen; The secondary endpoint: mortality; the proportion of patients alive and without respiratory failure | US FDA guidelines |
Mortality

1724 COVID-19 patients from 7 studies contribute to mortality data. GM-CSF antibodies were used in 847/1724 patients. As shown in Fig. 2, the risk of mortality in the GM-CSF antibody group was slightly lower than that in the control group, which was supported by two cohort studies (OR 0.24; 95% CI 0.04, 1.42) and five RCTs (OR 0.84; 95% CI 0.63, 1.10). Heterogeneity was low for both cohort studies and RCTs. Of note, the sensitive analysis further showed that the results of mortality based on RCTs become statistically significant (OR 0.73, 95% CI 0.55, 0.98, \( p = 0.04 \), Supplemental Table 3) when the study of Criner et al. 2022 was removed.

Incidence of invasive mechanical ventilation (IMV)

To estimate the risk of incidence of IMV, we analyzed the data of 822 COVID-19 patients from 5 studies, including 395 in the GM-CSF antibody group and 427 in the control group. As shown in Fig. 3, incidence of IMV in GM-CSF antibodies group was lower than that in control group, which was supported by two cohort studies (OR 0.16; 95% CI 0.03, 0.74) and three RCTs (OR 0.62; 95% CI 0.41, 0.94). Heterogeneity was low for both cohort studies and RCTs. The results are similar when excluding each one of these included studies (Supplemental Table 3).

Ventilation improvement rate

The rate of ventilation improvement (need oxygen therapy to without oxygen therapy) from 3 controlled clinical trial, involving 304 COVID-19 patients (147 in the GM-CSF antibodies treatment group and 157 in the control group), were analyzed. A total of 99/147 in the GM-CSF antibodies treatment group and 92/157 patients in control group had improved ventilation, respectively. As shown in Fig. 4, the treatment of GM-CSF antibodies did not significantly improve ventilation in patients, which was supported by one cohort study of De Luca et al. (2020) (OR 5.50; 95% CI 1.01, 29.85) and two RCTs (OR 2.02, 95% CI 0.34, 12.12). Besides, when excluded the study of Criner et al. 2022, the results of ventilation improvement rate based on the study of Criner et al. 2022 become statistically significant (OR 6.07, 95% CI 1.58, 23.33, \( p = 0.009 \), Supplemental Table 3).

Secondary infection

The data of secondary infection were from 6 studies involving 1718 patients. Among them, 854 patients were in the GM-CSF antibody group and 864 patients were in control.
group. As presented in Fig. 5, secondary infection was not found to differ significantly across groups, which was supported by both one cohort study (OR 0.25, 95% CI 0.01, 5.19) and five RCTs (OR 1.00, 95% CI 0.71, 1.41). Heterogeneity was low for both cohort studies and RCTs. The results are similar when excluding each one of these included studies (Supplemental Table 3).

**Fig. 2** Risk of mortality between GM-CSF antibodies and control groups

**Fig. 3** The risk of IMV between the GM-CSF antibodies treatment group and the control group in COVID-19 patients

### Adverse events

Among the included trials, five RCTs reported covering nine kinds of adverse events (AEs), four RCTs reported the total number of treatment patients with AEs, and four RCTs reported serious adverse events (SAEs). As shown in Table 2 and Supplementary Fig. 2, compared with control group, GM-CSF antibodies treatment did not increase the AE rate (OR 0.95, 95% CI 0.86, 1.05, P = 0.31) and SAE rate (OR 0.85, 95% CI 0.66, 1.08, P = 0.18). Of note, GM-CSF antibodies treatment was almost associated with the lower rate of
pulmonary AEs based on 2 trials involving 1305 COVID-19 patients (OR 0.99, 95% CI 0.59, 1.00, $P = 0.05$). Heterogeneity was low for both cohort studies and RCTs. The results are similar when excluding each one of these included studies (Supplemental Table 3).

**Discussion**

The COVID-19 pandemic remains an urgent problem around the globe, with the global outbreak still not fully contained and cases rising. Prior research indicates that patients with COVID-19 infection have increased levels of GM-CSF in their blood, especially in the later stages of the disease (Leavis et al. 2022). Previous studies revealed that GM-CSF can enhance the expression of many pro-inflammatory cytokines and chemokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (Becher et al. 2016). The anti-GM-CSF monoclonal antibodies might have broader effects than other immunomodulatory approaches on the systemic pro-inflammatory responses accompanying the cytokine release syndrome in COVID-19. In addition, the anti-GM-CSF monoclonal antibodies have been approved by the FDA for emergency compassionate use in COVID-19 patients (Humanigen, Inc. 2020).
Table 2  Adverse events between the GM-CSF antibodies treatment group with control group

|                      | Patel 2022 | Fisher 2022 | Cremer 2021 | Temesgen 2021 | Criner 2022 |
|----------------------|------------|-------------|-------------|---------------|-------------|
|                      | A          | B           | A           | B             | A           | B           | A           | B             |
| **Number of patients** | 397        | 396         | 55          | 54            | 21          | 19          | 255         | 257           | 113          | 112          |
| **Patients with AEs** | 274        | 265         | 30          | 29            | 10          | 10          | 5           | 4             | 47           | 45           |
| **Patients with SAEs**| 124        | 147         | 10          | 10            | 5           | 4           | 4           | 3             | 47           | 45           |
| **Gastrointestinal AEs** | 54         | 53          |             |               |             |             |             |               |              |              |
| Diarrhea             | 15         | 18          |             |               |             |             |             |               |              |              |
| Constipation         | 39         | 35          |             |               |             |             |             |               |              |              |
| **Liver function events** | 6          | 5           | 5           | 3             | 11          | 7           | 8           | 10            |
| ALT elevation        | 5           | 3           | 5           | 3             |             |             |             |               |              |              |
| GGT elevation        |             |             |             |               | 6           | 4           |             |               |              |              |
| Hepatocellular injury|           |             |             |               |             |             |             |               |              |              |
| Abnormal liver enzyme test |           |             |             |               |             |             |             |               | 8             | 10            |
| **Lung function event** | 69         | 85          | 66          | 80            |             |             |             |               |              |              |
| Respiratory failure  | 19         | 21          | 24          | 31            |             |             |             |               |              |              |
| Pulmonary embolism   | 13         | 25          | 5           | 3             |             |             |             |               |              |              |
| Hypoxemia            | 10         | 13          | 15          | 15            |             |             |             |               |              |              |
| Acute respiratory failure | 10        | 11          | 18          | 22            |             |             |             |               |              |              |
| Pneumothorax         | 17         | 15          | 0           | 6             |             |             |             |               |              |              |
| Acute respiratory distress syndrome | 4 | 3 | | | | | | | |
| **Cardiac disorders event** | 12 | 18 | 11 | 11 | 3 | 3 | | | |
| Atrial fibrillation  | 12         | 18          | 3           | 3             |             |             |             |               |              |              |
| Cardiac arrest       |             |             | 8           | 4             |             |             |             |               |              |              |
| Cardiorespiratory arrest |             |             | 3           | 4             |             |             |             |               |              |              |
| Acute myocardial infarction |             |             | 0           | 3             |             |             |             |               |              |              |
| **Renal function event** | 23         | 25          | 4           | 3             | 5           | 8           | 5           | 9             |
| Renal failure        |             |             |             |               | 2           | 0           |             |               |              |              |
| Acute kidney injury  | 23         | 25          | 4           | 3             | 5           | 8           | 3           | 9             |
| **Infection**        | 81         | 71          | 6           | 6             | 2           | 1           | 7           | 14            | 15           | 9            |
| Pneumonia            | 43         | 29          | 4           | 5             | 2           | 1           |             |               | 3           | 3            |
| Urinary tract infection | 13         | 14          |             |               |             |             |             |               |              |              |
| Septic shock         | 18         | 16          |             |               | 5           | 9           | 7           | 6             |             |              |
| Sepsis               | 7           | 12          | 2           | 1             | 2           | 5           | 5           | 0             |             |              |
| **Blood system**     | 18         | 22          | 6           | 6             |             |             |             |               |              |              |
| Anemia               | 18         | 22          | 6           | 6             |             |             |             |               |              |              |
| MODS                 | 12         | 16          | 1           | 3             |             |             |             |               | 3           | 6            |
| **Other adverse events** | 137        | 107         | 2           | 6             | 2           | 5           | 2           | 0             |
| Pyrexia              | 20         | 15          |             |               |             |             |             |               |              |              |
| Hypernatremia        | 20         | 10          | 1           | 1             |             |             |             |               |              |              |
| Hypokalemia          | 15         | 16          |             |               |             |             |             |               |              |              |
| Hyperkalemia         | 17         | 13          | 1           | 5             |             |             |             |               |              |              |
| Hypotension          | 14         | 16          |             |               | 2           | 5           |             |               |              |              |
| Hypertension         | 17         | 10          |             |               |             |             |             |               |              |              |
| Delirium             | 17         | 17          |             |               |             |             |             |               |              |              |
| Decubitus ulcer      | 16         | 9           |             |               |             |             |             |               |              |              |
| Infusion-related reaction | 1         | 1           |             |               |             |             |             |               | 2           | 0            |

A GM-CSF antibodies treatment group, B control group
Based on the considerable potential of GM-CSF antibodies to treat COVID-19, this article intends to evaluate the clinical efficacy and safety of GM-CSF antibodies for COVID-19. Our meta-analysis involved seven studies that examined GM-CSF antibodies as a treatment for COVID-19 patients, including two studies used anti-GM-CSFR antibodies and the other five studies used anti-GM-CSF antibodies. We found that: (1) treatment with GM-CSF antibodies decreased the incidence of IMV; (2) GM-CSF antibodies resulted in a slight but not significant decrease in mortality and the ventilation improvement rate, while sensitive analysis showed that the results of mortality and ventilation improvement rate became statistically significant when one included study were removed; (3) GM-CSF antibodies did not increase risks of secondary infection and AEs in COVID-19 patients. Taken together, our study suggests that GM-CSF antibodies is well tolerated and may have substantial effects in reducing the incidence of IMV among COVID-19 patients. Further studies on the beneficial effects of GM-CSF antibodies in COVID-19 patients remain needed, especially for mortality and the ventilation improvement rate.

GM-CSF antibodies inhibit the GM-CSF signaling axis by targeting GM-CSF, or GM-CSFR. Both strategies blocked the same interaction regardless of whether they targeted GM-CSF or GM-CSFR in theory (Zhou et al. 2020). In our meta-analysis, the treatment with GM-CSF antibodies (pooled the data of both strategies together) mainly decreased the incidence of IMV but only slightly affected mortality and ventilation improvement rate. Two of our included articles used mavrilimumab, the monoclonal antibody against GM-CSFR, which has a similar effect to GM-CSF target antibodies for decreasing the incidence of IMV the treatment of COVID-19. However, results of mortality and ventilation improvement rate became statistically significant after removing Criner et al. 2022, one of the RCTs used mavrilimumab. These results indicate the type of GM-CSF antibodies remains the potential factor contributing to the heterogeneities and might influence the efficacy of GM-CSF antibodies treatment for COVID-19 patients.

Secondary infection often indicates severe severity and results in mortality in COVID-19 patients (Guo et al. 2021). Secondary infection is also common side effects or AEs of many anti-inflammatory therapies, such as glucocorticoid, Janus kinase inhibitors, and IL-6 antibodies (Russell et al. 2020; Shah et al. 2022; Winthrop et al. 2018). Kimmig et al. (2020) and Quartuccio et al. (2020) revealed that COVID-19 patients used IL-6 antibodies may have a higher rate of secondary infection; Roumier et al. (2021) also reported that early inhibition of IL-6 may trigger many AEs in COVID-19 patients. Different from IL-6 antibodies, here we found that GM-CSF inhibition treatment did not increase the risks of secondary infection and other AEs in COVID-19 patients. Besides, GM-CSF antibodies treatment was almost significantly reduced the rate of pulmonary AEs in COVID-19 patients. Thus, GM-CSF inhibition treatment might be safer than IL-6 antibodies and other anti-inflammatory therapies.

Several limitations in our meta-analysis should be noted as follows: (1) Funnel-plot analysis and Egger’s test were not performed because of the small number of included studies. (2) One study is a pre-publication, which can lead to publication bias or other potential risks. Two of the seven studies are nonrandomized, which may reduce the credibility of the combined results (though we analyzed the nonrandomized studies and RCTs separately). (3) The different standards of care used in these studies prevent us from conducting an adequate comparison and analysis. As an example, oxygen therapy and nursing measures may influence mortality in COVID-19 patients. (4) The study population is different for some studies, which implies a risk of selection bias. (5) Moreover, there are some other factors influencing the results in this study, such as other drugs, ventilator availability, and vaccines. The synergistic effect or other interactions of these factors (such as dexamethasone (Vohra et al. 2021)) remain unclear.

Conclusions

Our meta-analysis shows treatment with GM-CSF antibodies decreased the incidence of IMV and does not increase the risks of second infection and AEs. It is likely that GM-CSF antibodies reduced mortality and the ventilation improvement rate. Further RCTs, cohort studies, and multicenter clinical studies are still needed.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10787-022-01105-9.

Author contributions The study was designed by JG and ZX; AX and YL ran the search strategies and undertook the search. JG and WW extracted data and analysis. AX and YL wrote the manuscript. AX, YL, JG and WW contribute to editing the manuscript and checking all the extracted data under the supervision of ZX.

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Data availability All data are presented in the text.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval Consent statement and ethical approval are not required as the current study was based on published data.
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