Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): an investigator initiated, multicentre, double-blind, randomised, placebo-controlled trial

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Summary

Background In patients with COVID-19, granulocyte-macrophage colony stimulating factor (GM-CSF) might be a mediator of the hyperactive inflammatory response associated with respiratory failure and death. We aimed to evaluate whether mavrilimumab, a monoclonal antibody to the GM-CSF receptor, would improve outcomes in patients with COVID-19 pneumonia and systemic hyperinflammation.

Methods This investigator-initiated, multicentre, double-blind, randomised trial was done at seven hospitals in the USA. Inclusion required hospitalisation, COVID-19 pneumonia, hypoxaemia, and a C-reactive protein concentration of more than 5 mg/dL. Patients were excluded if they required mechanical ventilation. Patients were randomly assigned (1:1) centrally, with stratification by hospital site, to receive mavrilimumab 6 mg/kg as a single intravenous infusion, or placebo. Participants and all clinical and research personnel were masked to treatment assignment. The primary endpoint was the proportion of patients alive and off supplemental oxygen therapy at day 14. The primary outcome and safety were analysed in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, NCT04399980, NCT04463004, and NCT04492514.

Findings Between May 28 and Sept 15, 2020, 40 patients were enrolled and randomly assigned to mavrilimumab (n=21) or placebo (n=19). A trial of 60 patients was planned, but given slow enrolment, the study was stopped early to inform the natural history and potential treatment effect. At day 14, 12 (57%) patients in the mavrilimumab group (n=21) or placebo (n=19). A trial of 60 patients was planned, but given slow enrolment, the study was stopped early to inform the natural history and potential treatment effect. At day 14, 12 (57%) patients in the mavrilimumab group were alive and off supplemental oxygen therapy compared with nine (47%) patients in the placebo group (odds ratio 1.48 [95% CI 0.43–5.16]; p=0.76). There were no treatment-related deaths, and adverse events were similar between groups.

Interpretation There was no significant difference in the proportion of patients alive and off oxygen therapy at day 14, although benefit or harm of mavrilimumab therapy in this patient population remains possible given the wide confidence intervals, and larger trials should be completed.

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Introduction

For people infected with SARS-CoV-2, the cause of COVID-19, there are few effective treatments. Early disease manifestations are related to viral replication and immune cell-mediated death in respiratory epithelial cells. As viral replication wanes after the first week of infection, a subset of patients develop a hyperactive immune response that perpetuates lung injury, and most deaths occur in patients with heightened systemic inflammation who develop acute respiratory distress syndrome. As viral replication wanes after the first week of infection, a subset of patients develop a hyperactive immune response that perpetuates lung injury, and most deaths occur in patients with heightened systemic inflammation who develop acute respiratory distress syndrome. In the lungs, GM-CSF activates alveolar macrophages to promote clearance of respiratory microbes through production of pro-inflammatory cytokines, but the resultant feed-forward inflammatory loop might promote further damage. In a large, randomised trial, broad immunosuppression with dexamethasone improved mortality in patients with severe or critical COVID-19 pneumonia, supporting the importance of hyperinflammation in adverse outcomes. Observational studies have also suggested a potential benefit with GM-CSF antagonism in patients with COVID-19 pneumonia and heightened systemic inflammation.
Mavrilimumab is a monoclonal antibody that binds to the α subunit of the GM-CSF receptor and blocks intracellular signalling downstream of GM-CSF. Based on this mechanism of action, the putative role of increased GM-CSF in adverse outcomes from COVID-19, and encouraging results from an observational study of patients with COVID-19 pneumonia and hyperinflammation treated with mavrilimumab, we aimed to test the hypothesis that treatment with mavrilimumab would lead to better clinical outcomes in patients with COVID-19 pneumonia, hypoxaemia, and hyperinflammation. The primary hypothesis was that a higher proportion of patients treated with mavrilimumab would not require oxygen at day 14, compared with patients treated with placebo. The secondary hypothesis was that patients treated with mavrilimumab would have improved survival and more freedom from respiratory failure at day 28. A favourable signal for efficacy from this study could inform a larger trial.

Methods

Study design and participants

The MASH-COVID study is an investigator-initiated, multicentre, double-blind, randomised, placebo-controlled trial that was done at seven hospitals in the USA (three referral centres and four community hospitals; appendix p 1). Inclusion required inpatient hospitalisation for COVID-19; documented COVID-19 pneumonia defined as a positive upper respiratory tract specimen for SARS-CoV-2 with associated abnormalities or infiltrates on chest x-ray or chest CT; active fever or documented fever within 48 h or antipyretic use; hypoxaemia, defined as a room air oxygen saturation of less than 92% or requirement of supplemental oxygen; and a C-reactive protein concentration greater than 5 mg/dL. Notable exclusion criteria included age younger than 18 years, absolute neutrophil count less than 1500/mm³, home oxygen therapy, mechanical ventilation, uncontrolled systemic bacterial infection, and onset of symptoms more than 14 days before hospital admission and enrolment (full inclusion and exclusion criteria are listed in the appendix pp 1–3).

The design and conduct of the study were approved by the US Food and Drug Administration. The trial was done according to the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice Guidelines. The trial was overseen by a data monitoring committee with details described in a separate charter. The data monitoring committee assessed safety and made no formal assessment of efficacy. The protocol was approved by the Institutional Review Board at each site, and written informed consent was obtained from all patients or their legally authorised representative. Data management was coordinated by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research; Cleveland, OH, USA). Data were entered into a secure REDCap Cloud database, and analysis was done by C5Research. The study protocol is in the appendix pp 21–59.

Randomisation and masking

Patients were randomly assigned (1:1) to receive mavrilimumab or placebo. Randomisation was centralised through REDCap Cloud with stratification by hospital site. The participants and all clinical and research personnel were masked to treatment assignment, except for a research pharmacist who prepared the mavrilimumab infusion or equal volume infusion of diluent for placebo. This research pharmacist did not participate in the administration of the infusion. Irrespective of their participation in the study, enrolled patients received...
COVID-19 therapies considered appropriate by their clinicians.

**Procedures**

Mavrilimumab 6 mg/kg was administered as a single intravenous infusion. For placebo, an equal volume of diluent was given intravenously via the same infusion pump that was used for mavrilimumab. The investigator was required to discontinue treatment if continuation would negatively affect a participant’s wellbeing. After study discontinuation, the participant would remain in the study unless consent was withdrawn. Reasons for study discontinuation could include patient or surrogate request, pregnancy, use of prohibited treatment (appendix p 2), any safety risk to the patient, and any laboratory abnormalities that in the judgment of the investigator would prevent the patient from continuing. Following enrolment, adverse events and clinical status including the ordinal scale were assessed daily until discharge as well as at day 7, 14, 21, 28, and 60. Information on concomitant medications was collected at baseline and daily until day 7, and then at days 14, 21, and 28. Concomitant medications included antiviral drugs related to COVID-19, corticosteroids, convalescent plasma, other immunosuppressive agents, and antimicrobial drugs related to non-COVID-19 infections. Follow-up laboratory testing was done according to clinical standard of care, in alignment with institutional policies for caregiver safety and conservation of personal protective equipment, and accordingly was not uniform across all patients and sites. Follow-up laboratory testing was also not done after patient discharge.

**Outcomes**

The primary efficacy outcome was the proportion of patients alive and off supplemental oxygen therapy at day 14 after infusion of mavrilimumab or placebo. The secondary endpoints were the proportion of patients alive at day 28, and the proportion of patients alive and without respiratory failure at day 28. Respiratory failure was defined as a requirement for mechanical ventilation, non-invasive ventilation, or high-flow oxygen. Primary and secondary outcomes were assessed in the intention-to-treat population. An assessment for interaction between treatment group and corticosteroid or remdesivir use was prespecified. The first exploratory endpoint was the time to clinical improvement up to day 14 or day 28, defined as time from randomisation to an improvement of two points on a seven-category ordinal scale or discharge from the hospital. The ordinal scale was modified from an original model proposed by WHO by removing the category uninfected, combining categories of ventilation and ventilation plus additional organ support, and substituting resumption of normal activities with need for oxygen therapy. The modified categories were (1) not hospitalised and not on supplemental oxygen; (2) not hospitalised but on supplemental oxygen; (3) hospitalised, not requiring supplemental oxygen; (4) hospitalised, requiring supplemental oxygen; (5) hospitalised, requiring nasal high-flow oxygen or non-invasive mechanical ventilation, or both; (6) hospitalised, requiring invasive mechanical ventilation, extracorporeal membrane oxygenation, or both; and (7) death. The other exploratory endpoints were proportion of patients in each category of the ordinal scale at day 7, 14, 21, and 28; mortality at day 60; mortality at day 14; need for mechanical ventilation; duration of hospitalisation; changes in the ratio of arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2) at day 3, 5, 7, 14, 21, and 28, or until discharge; change in the Sequential Organ Failure Assessment (SOFA) score at day 7, 14, 21, and 28, or until discharge; reduction in C-reactive protein concentration at day 7 and 14; and time to negative SARS-CoV-2 RNA concentrations in oropharyngeal or nasopharyngeal swabs. After randomisation, subsequent daily PaO2 to FiO2 ratios were selected as the lowest value over the 24 h period beginning at midnight. All exploratory outcomes were assessed in all patients for whom follow-up data were available.

Safety and adverse events were assessed by the principal investigator during the hospital admission. The principal investigator assessed all new clinical diagnoses and abnormal laboratory results to determine whether they were adverse events, and whether they were serious adverse events, treatment-related adverse events, or both. The severity of the event was also assessed. After patient discharge, safety and adverse events were assessed by research personnel during telemedicine visits.

**Statistical analysis**

Estimates of the efficacy of mavrilimumab in this patient population are scarce and, based on preliminary case-control data of patients with severe COVID-19 pneumonia treated with mavrilimumab, it was estimated that 40% of patients in the placebo group would meet the

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**Figure 1: Trial profile**

159 patients screened
40 randomly assigned
21 allocated to mavrilimumab
19 allocated to placebo
21 received mavrilimumab
19 received placebo
21 included in analyses of primary and secondary outcomes
19 included in analyses of primary and secondary outcomes
1 lost to follow-up (missed visit)
primary endpoint compared with 80% of patients treated with mavrilimumab. Therefore, a sample size of 30 patients per group (60 total) would provide 80% power to detect this difference using a two-sided α error of 0.05. However, due to slow enrolment after the first surge of COVID-19, the study was concluded after enrolment of 40 patients, in the interest of having a more accurate measure of event rate in the control group and an estimate of effect size in the treatment group. Between-group comparisons were done with t tests, Wilcoxon rank sum tests, χ² tests, and Fisher exact tests, as appropriate. The magnitude of effect for the primary and secondary endpoints is expressed using the odds ratio (OR) with 95% CI. The time to clinical improvement was assessed with a log-rank test between mavrilimumab and placebo. Adjusted recovery rate ratios (RRRs) with 95% CIs were calculated from a Cox proportional hazards model. The RRR is similar to the hazard ratio (HR) in survival analysis except for the beneficial outcome of clinical improvement; therefore, an RRR greater than 1 indicates clinical improvement. HRs for mortality were also calculated from a Cox proportional hazards model. No adjustments were made for multiple hypothesis testing. Given the early termination of the study, nominal p values are descriptive, and all results should be considered hypothesis-generating. QW and KEW did the statistical analyses. Analyses were done using SAS version 9.4. The statistical analysis plan is in the appendix pp 4–20. This trial is registered at ClinicalTrials.gov, NCT04399980, NCT04463004, and NCT04492514.

Role of the funding source

The funder of the study provided the study drug, facilitated formation of the investigator consortium, assisted with study design and interpretation of the data, and had a role in editing the report. The investigator consortium and the funder conceived of the study. The funder of the study had no role in data analysis or data collection.

Results

Between May 28 and Sept 15, 2020, 40 patients were enrolled and randomly assigned to a treatment group (mavrilimumab n=21, placebo n=19; figure I). All patients completed the allocated intervention. One patient in the placebo group completed the allocated intervention. One patient in the placebo group did not complete the allocated intervention. Before random assignment, 26 (65%) of 40 patients were treated with corticosteroids, including 14 (67%) of 21 patients who received mavrilimumab and 12 (63%) of 19 patients who received placebo. After random assignment, an additional five patients were started on corticosteroids (two in the mavrilimumab group, three in the placebo group). For patients enrolled before July 1, 2020, three (25%) of 12 patients across both groups were treated with corticosteroids. After publication of the RECOVERY trial in July, 2020, all 28 (100%) subsequently

| Table 1: Baseline characteristics of patients in the intention-to-treat population |
|---------------------------------|-----------------|-----------------|-----------------|
| | Total (n=40) | Mavrilimumab group (n=21) | Placebo group (n=19) |
| Age, years | 56.7 (44.9–68.7) | 54.8 (49.7–68.1) | 59.0 (41.0–69.3) |
| Sex | | | |
| Male | 26 (65%) | 14 (67%) | 12 (63%) |
| Female | 14 (35%) | 7 (33%) | 7 (37%) |
| Race | | | |
| African-American | 16 (40%) | 8 (38%) | 8 (42%) |
| White | 19 (48%) | 11 (52%) | 8 (42%) |
| Other | 5 (13%) | 2 (10%) | 3 (16%) |
| Ethnicity | | | |
| Hispanic or Latino | 6 (15%) | 3 (14%) | 3 (16%) |
| Body-mass index, kg/m² | 32.7 (29.0–38.1) | 30.3 (27.2–41.1) | 32.7 (30.5–35.5) |
| Comorbidities | | | |
| Diabetes | 17 (43%) | 8 (38%) | 9 (47%) |
| Hypertension | 22 (55%) | 10 (48%) | 12 (63%) |
| Hyperlipidaemia | 18 (45%) | 7 (33%) | 11 (58%) |
| Coronary artery disease | 4 (10%) | 1 (5%) | 3 (16%) |
| Stroke | 1 (3%) | 0 | 1 (5%) |
| Chronic obstructive pulmonary disease | 3 (8%) | 3 (14%) | 0 |
| Chronic kidney disease | 3 (8%) | 1 (5%) | 2 (11%) |
| Current or former smoker | 11 (28%) | 7 (33%) | 4 (21%) |
| Time from symptom onset to hospitalisation, days | 9 (6–11) | 9 (6–10) | 9 (7–11) |
| D-dimer, ng/mL§ | 890 (430–1270) | 860 (470–1200) | 900 (410–1270) |
| Ferritin, ng/mL‡ | 1040 (486–1860) | 1122 (410–2523) | 1000 (499–1728) |
| C-reactive protein concentration, mg/dL* | 13·1 (9·8–18·8) | 14·0 (9·9–18·8) | 12·3 (9·4–19·4) |
| Lymphocyte count, thousand cells per µL† | 1·1 (0·7–1·3) | 1·0 (0·8–1·2) | 1·1 (0·6–1·3) |
| Ferritin, ng/mL‡ | 1040 (486–1860) | 1122 (410–2523) | 1000 (499–1728) |
| D-dimer, ng/mL§ | 890 (430–1270) | 860 (470–1200) | 900 (410–1270) |

Data are median (IQR) or n (%). Percentages might not total 100% due to rounding. FiO₂=fractional inspired oxygen. PaO₂=arterial oxygen partial pressure. SOFA=Sequential Organ Failure Assessment. *Reference range 0·0–0·4 mg/dL. §Reference range 0·0–5·0 mg/dL. ‡Reference range 0·0–1·0 mg/dL. †Reference range 1·0–4·0 thousand cells per µL. 

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enrolled patients across both groups were treated with corticosteroids. Before random assignment, 30 (75%) of 40 patients were treated with remdesivir, including 16 (76%) of 21 patients who received mavrilimumab and 14 (74%) of 19 patients who received placebo. After random assignment, three patients received remdesivir (two in the mavrilimumab group, one in the placebo group); ten patients received convalescent plasma (four in the mavrilimumab group, six in the placebo group); and two patients received tocilizumab (one in each group).

There was no significant difference between the groups in the proportion of patients who were alive and off supplemental oxygen therapy by day 14 (OR 1.48 [95% CI 0.95–2.29]; p=0.08; table 2). There was no significant interaction between treatment group and proportion of patients who were alive and off supplemental oxygen with corticosteroid use (OR 1.29 [0.26–6.27]) or remdesivir use (3.21 [0.70–14.74]). At day 28, there was no significant difference between the groups in the proportion of patients who were alive and without respiratory failure (OR 0.53 [0.34–0.84]; table 2). There was no significant interaction between treatment group and the proportion of patients who were alive and without respiratory failure with corticosteroid use (OR 1.29 [0.26–6.27]) or remdesivir use (1.71 [0.40–7.29]). By day 28, one (5%) patient treated with mavrilimumab had died compared with three (16%) patients treated with placebo (HR 3.72 [95% CI 0.39–35.79]; table 2).

There was no significant difference in time to clinical improvement up to day 28 for patients treated with mavrilimumab compared with placebo (median 5 days [95% CI 3–7] vs 6 days [4–10]; RRR 1.47 [95% CI 0.43–5.16]; table 2). There were no treatment related deaths. In the intention to treat population (n=40), adverse events and abnormal laboratory values were similar between the two groups (table 3). There were no infusion reactions, and no patient developed neutropenia. In addition, no patients developed bacteraemia. Bacterial pneumonia was diagnosed in one patient who received placebo (5%) and two patients who received mavrilimumab (10%).

### Discussion

The MASH-COVID study was designed as an early signal of efficacy trial to assess whether GM-CSF inhibition with mavrilimumab would improve clinical outcomes in patients with severe COVID-19 pneumonia and increased systemic inflammation. There was no significant difference between the groups for the primary endpoint, although patients who received mavrilimumab were numerically more likely to be alive and off oxygen at day 14 than were patients who received placebo. In addition, by day 28, patients who received mavrilimumab were numerically more likely to be alive and without respiratory failure than were patients who received placebo.
placebo. In comparison with the initial statistical analysis plan, more patients in the placebo group than anticipated were off supplemental oxygen therapy by day 14, the relative risk reduction with mavrilimumab was lower than predicted, and enrolment was stopped due to slower than expected recruitment after the first surge of COVID-19, with the intent of gathering an earlier estimate of effect size to inform larger studies. There were no safety concerns noted with mavrilimumab in this trial, even with a high proportion of patients on concomitant corticosteroids.

GM-CSF is produced mainly at sites of inflammation via cell types such as epithelial cells, fibroblasts, endothelial cells, macrophages, dendritic cells, T cells, and neutrophils, increasing the inflammatory reaction via cytokine pathways that have been termed the colony stimulating factor network. In patients with COVID-19, GM-CSF plasma concentrations are elevated compared with healthy control samples, and GM-CSF-activated macrophages produce pro-inflammatory cytokines, including tumour necrosis factor (TNF), IL-1β, IL-6, IL-23, and IL-12. Mavrilimumab is an anti-GM-CSF-Rα monoclonal antibody (human isoform IgG4) that has been shown to inhibit the GM-CSF signalling axis in humans and to improve clinical outcomes in phase 2 trials in patients with rheumatoid arthritis and giant cell arteritis. With regard to
mitigation of the aberrant immune response in the setting of COVID-19 pneumonia, it is unclear whether blockade of GM-CSF in the lung is required in addition to ablation of signalling in the periphery. Preclinical data suggested that a dose higher than that needed to achieve 100% receptor occupancy in circulation (3 mg/kg) might be required to achieve therapeutic inhibitory concentrations in the lung. Therefore, a dose of 6 mg/kg administered intravenously was selected to assess the pharmacodynamic effects in the lung to inhibit the inappropriate innate immune response and reduce further lung injury.

Results from an observational study by De Luca and colleagues of patients hospitalised with COVID-19 pneumonia and systemic hyperinflammation suggested a possible benefit in patients who received mavrilimumab. Specifically, during 28-day follow-up, none of the 13 patients who received mavrilimumab died compared with seven of the 26 participants in the historical control group. All the patients who received mavrilimumab and 65% of patients in the control group showed clinical improvement. Patient age and C-reactive protein elevations were similar between De Luca and colleagues’ study and the MASH-COVID trial. However, in our study, mean baseline PaO2 to FiO2 ratio was lower: 138 in the study and the MASH-COVID trial. However, in our study, elevations were similar between De Luca and colleagues’ improvement. Patient age and C-reactive protein
group. All the patients who received mavrilimumab and 13 patients who received mavrilimumab died compared with 217 in the placebo group of MASH-COVID compared with 217 in the control group of the observational study. In MASH-COVID, 79% of patients in the placebo group were alive and without respiratory failure at day 28. Although speculative, despite more severe hypoxaemia in the MASH-COVID than in the study by De Luca and colleagues, the better than expected outcomes in the placebo group of MASH-COVID might reflect improvements in patient care and efficacy of concomitant medications, including corticosteroids and remdesivir, as opposed to background therapy of lopinavir–ritonavir and hydroxychloroquine used in the observational study.

Several randomised trials have evaluated therapies that inhibit the innate immune response in patients with COVID-19, although understanding of the potential efficacy of these therapies is incomplete in terms of the severity of illness most likely to respond, the magnitude of systemic hyperinflammation necessary to derive a benefit, the timing and duration of the intervention, the breadth of immunosuppression required, and the role of concomitant therapies. With respect to the degree of illness, patients with more severe hypoxaemia might be more likely to respond to therapies that inhibit the innate immune response. Data from the RECOVERY Collaborative group showed that patients with COVID-19 requiring invasive mechanical ventilation derived the greatest benefit from dexamethasone, followed by non-intubated patients receiving oxygen, whereas patients who did not require oxygen at baseline did not accrue a survival benefit. In the BACC Bay study, tocilizumab was not effective in preventing intubation or death in patients with COVID-19, but patients requiring more than 10 L nasal cannula oxygen were excluded from the study. Conversely, in the EMPACTA trial, although there was no difference in survival, patients with COVID-19 who received tocilizumab were less likely to require invasive ventilation than those who did not, and approximately a quarter were receiving high-flow oxygen or non-invasive ventilation at baseline. Moreover, data from the ADAPTIVE and RECOVERY platforms showed better outcomes with IL-6 antagonists in some patients with COVID-19, although peer-reviewed data from the RECOVERY trial are not yet published.

The degree of systemic inflammation is also likely to be important, and in a systematic review, circulating concentrations of IL-6 in many patients with COVID-19 were lower than in patients with acute respiratory distress syndrome or septic shock. Therefore, the wide spectrum of disease severity in patients with COVID-19 is important to recognise, and there are probably different patterns of immunopathology within COVID-19. In particular, trials with tocilizumab and sarilumab that did not require patients to have increased systemic inflammation for inclusion might not have targeted the ideal patient population (NCT04320615, NCT04327388). The breadth of immunosuppression required might also be crucial, and there might be a benefit to upstream antagonism of GM-CSF. The role of concomitant therapies should also be emphasised. Data from the ACTT-2 study group showed that combination treatment with baricitinib, a Janus kinase inhibitor, plus remdesivir shortened time to recovery, particularly among patients with COVID-19 receiving high-flow oxygen or non-invasive ventilation. However, only a minority of patients in that study were receiving corticosteroids. Therefore, whether targeted therapies provide benefit beyond dexamethasone, which is widely available and inexpensive, is an important clinical question. Such investigations might require an adjustment in sample size due to lower-than-expected event rates in the control group and a related smaller benefit of add-on therapies. Nevertheless, despite the benefits of dexamethasone, the mortality of patients with severe and critical COVID-19 disease is unacceptably high.

### Table 3: Adverse events and selected laboratory safety data in the intention-to-treat population

| Event                                | Mavrilimumab group (n=21) | Placebo group (n=19) |
|--------------------------------------|---------------------------|---------------------|
| Any serious adverse event            | 5 (24%)                   | 4 (21%)             |
| Circulatory shock                    | 2 (10%)                   | 1 (5%)              |
| Acute kidney injury                  | 4 (19%)                   | 3 (16%)             |
| Bacterial pneumonia                  | 2 (10%)                   | 1 (5%)              |
| Bacteraemia                          | 0                         | 0                   |
| Neutropenia                          | 0                         | 0                   |
| Alanine aminotransferase more than 3 times normal value | 5 (24%) | 3 (16%) |
| Aspartate aminotransferase more than 3 times normal value | 6 (29%) | 4 (21%) |
Given the widespread use of dexamethasone, there are also concerns about the use of dual anti-inflammatory medications and the potential for more profound immunosuppression in a patient population at risk for secondary infections. Therefore, future studies could also consider formally evaluating the potential efficacy of GM-CSF antagonism in patients who have disease progression despite dexamethasone, a clinical scenario applicable to some patients enrolled in the MASH-COVID study.

The MASH-COVID study has notable limitations. As emphasised, the study is small, hypothesis-generating, and subject to type II error. Due to slow recruitment, enrolment was stopped after 40 of a planned 60 patients, in part to assess for an efficacy signal to inform a larger trial (NCT04447469). Likewise, although an advantage of our study is high background corticosteroid and remdesivir use, the interaction analyses with treatment and outcome were underpowered. In addition, exploratory analyses evaluating changes in inflammatory markers were initially planned, but collection of laboratory test results varied between patients. However, this investigator-initiated study was done during a time of resource limitation with an emphasis on protection of health-care workers and conservation of personal protective equipment. Therefore, blood draws and patient contact were restricted to clinical care. Moreover, given infection control considerations, patients did not return to the hospital for laboratory testing after discharge. In addition, a C-reactive protein concentration of more than 5 mg/dL was required for inclusion, although more marked elevations or use of other inflammatory markers such as ferritin or lactate dehydrogenase might be useful in identifying future patients most likely to benefit from mavrilimumab. The balance of baseline characteristics and other treatments is inherently difficult in small trials, and this is especially relevant with evolving therapeutic approaches to COVID-19. For example, a minority of patients were treated with corticosteroids before publication of the dexamethasone data from the RECOVERY collaborative group, whereas all patients recruited after publication received corticosteroids, although an interaction between corticosteroids and outcomes was not observed in MASH-COVID.

Mavrilimumab did not show a statistically significant increase in the proportion of patients free of supplemental oxygen at day 14 among those with severe COVID-19 pneumonia, hypoxaemia, and systemic hyperinflammation, although this positive outcome was numerically more likely in patients treated with mavrilimumab. By day 28, patients who received mavrilimumab were also numerically more likely to be alive and without respiratory failure. Based on these hypothesis-generating results, larger trials should be completed.

Contributors
All authors participated in reviewing and editing the manuscript and approved the submitted draft. All authors critically reviewed the manuscript and had final responsibility for the decision to submit for publication. PCC, QW, and KEW have verified the underlying data and had access to all the data in the study. PCC, AA, KH, SYC, PR, AD, TSW, JFP, and BCT conceived and designed the study. PCC, AA, KH, CM, JM, SYC, CCS, BVT, AB, AV, BC, QW, KEW, PR, AD, TSW, JFP, and BCT collected, analysed and interpreted the data. PCC, AA, KH, and JFP drafted the manuscript. PCC, QW, and KEW did the statistical analysis. PCC, AA, KH, SYC, CCS, AB, AV, BC, QW, KEW, PR, AD, TSW, JFP, and BCT critically revised the manuscript for important intellectual content. PCC supervised the study.

Declaration of interests
PCC has served on scientific advisory committees for Sohi and Kiniksa pharmaceuticals, and has received an investigator-initiated grant from Novartis pharmaceuticals, all outside the submitted work; PCC also received an investigator-initiated grant from Kiniksa to conduct the submitted work. AA has received research support from and served as an advisor to Kiniksa, outside the submitted work; SYC has served as a consultant for Pure Tech and has received support as a speaker for La Jolla Pharmaceuticals, outside the submitted work. AB and AV have received a travel grant from Kiniksa Pharmaceuticals and receive honoraria from Effetti (Milan, Italy) to collaborate on the Inflammology medical website, outside the submitted work. BVT has received grants from Kiniksa Pharmaceuticals, outside the submitted work. JFP is an employee and stockholder of Kiniksa Pharmaceuticals, and is an inventor on patent applications related to mavrilimumab. BCT has received personal fees from Kiniksa Pharmaceuticals, outside the submitted work. All other authors declare no competing interests.

Data sharing
The statistical analysis plan (appendix pp 4–20) and the study protocol (appendix pp 21–59) are available. Other study documents, including individual patient level data, are not available.

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