Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Lenzilumab in hospitalised patients with COVID-19 pneumonia (LIVE-AIR): a phase 3, randomised, placebo-controlled trial

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Summary

Background The pathophysiology of COVID-19 includes immune-mediated hyperinflammation, which could potentially lead to respiratory failure and death. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is among cytokines that contribute to the inflammatory processes. Lenzilumab, a GM-CSF neutralising monoclonal antibody, was investigated in the LIVE-AIR trial to assess its efficacy and safety in treating COVID-19 beyond available treatments.

Methods In LIVE-AIR, a phase 3, randomised, double-blind, placebo-controlled trial, hospitalised adult patients with COVID-19 pneumonia not requiring invasive mechanical ventilation were recruited from 29 sites in the USA and Brazil and were randomly assigned (1:1) to receive three intravenous doses of lenzilumab (600 mg per dose) or placebo delivered 8 h apart. All patients received standard supportive care, including the use of remdesivir and corticosteroids. Patients were stratified at randomisation by age and disease severity. The primary endpoint was survival without invasive mechanical ventilation to day 28 in the modified intention-to-treat population (mITT), comprising all randomised participants who received at least one dose of study drug under the documented supervision of the principal investigator or sub-investigator. Adverse events were assessed in all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT04351152, and is completed.

Findings Patients were enrolled from May 5, 2020, until Jan 27, 2021. 528 patients were screened, of whom 520 were randomly assigned and included in the intention-to-treat population. 479 of these patients (n=236, lenzilumab; n=243, placebo) were included in the mITT analysis for the primary outcome. Baseline demographics were similar between groups. 311 (65%) participants were males, mean age was 61 (SD 14) years at baseline, and median C-reactive protein concentration was 79 (IQR 41–137) mg/L. Steroids were administered to 449 (94%) patients and remdesivir to 347 (72%) patients; 331 (69%) patients received both treatments. Survival without invasive mechanical ventilation to day 28 was achieved in 198 (84%; 95% CI 79–89) participants in the lenzilumab group and in 190 (78%; 72–83) patients in the placebo group, and the likelihood of survival was greater with lenzilumab than placebo (hazard ratio 1·54; 95% CI 1·02–2·32; p=0·040). 68 (27%) of 255 patients in the lenzilumab group and 84 (33%) of 257 patients in the placebo group experienced at least one adverse event that was at least grade 3 in severity based on CTCAE criteria. The most common treatment-emergent adverse events of grade 3 or higher were related to respiratory disorders (26%) and cardiac disorders (6%) and none led to death.

Interpretation Lenzilumab significantly improved survival without invasive mechanical ventilation in hospitalised patients with COVID-19, with a safety profile similar to that of placebo. The added value of lenzilumab beyond other immunomodulators used to treat COVID-19 alongside steroids remains unknown.

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See Comment page 223

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See Online for appendix

Introduction

The clinical manifestations of COVID-19 can extend to critical illness, acute respiratory distress syndrome (ARDS), and death. These sequelae result from the viral-induced hyperinflammatory immune response, with granulocyte-macrophage colony-stimulating factor (GM-CSF) being among other cytokines involved in the redundant inflammatory processes characterised by activation and trafficking of myeloid cells,[1] leading to elevations of downstream inflammatory chemokines (macrophage chemotactic protein 1, interleukin 8 [IL-8], interferon gamma induced protein 10), cytokines (IL-6, IL-1),[2] and markers of systemic inflammation (C-reactive protein [CRP], D-dimer, ferritin).

In COVID-19, high levels of GM-CSF have been associated with disease severity, myeloid cell trafficking to

Research in context

Evidence before this study

A MEDLINE and Cochrane Central Register of controlled trials was evaluated. The terms "granulocyte-macrophage colony stimulating factor", "COVID-19", "cytokine storm", "cytokine release syndrome", "hyperinflammatory immune response", "hospitalization", "ventilation-free survival", "outcomes", and "clinical trials" were used to search for articles published up to June, 2020, with no restrictions to language. No completed randomised clinical trials were identified. One small case-controlled study, which made use of the neutralising anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) monoclonal antibody lenzilumab was reported to show improvement in COVID-19 outcomes. Several publications highlighted poor clinical outcomes associated with the hyperinflammatory immune response of COVID-19. The hyperinflammatory immune response, associated with SARS-CoV-2 infection and characterised by elevated markers of systemic inflammation, was implicated in disease progression to acute respiratory distress syndrome, multi-organ failure, and death. The potential of various immunomodulator agents to affect the COVID-19-related hyperinflammatory immune response was under active investigation during the period up to June, 2020, and beyond. GM-CSF is an upstream mediator of the hyperinflammatory immune response in COVID-19 and neutralisation of GM-CSF presented a novel therapeutic approach to prevent or treat COVID-19 disease progression alongside corticosteroids and antiviral remdesivir therapy.

Added value of this study

LIVE-AIR showed that treatment with intravenous lenzilumab, an anti-GM-CSF monoclonal antibody, significantly improved the likelihood of survival without invasive mechanical ventilation to day 28 in hospitalised patients with COVID-19 pneumonia.

Implications of all the available evidence

Lenzilumab significantly improved survival without invasive mechanical ventilation in hospitalised patients with COVID-19 who were treated concurrently with other available therapies; however, the added value of lenzilumab beyond other immunomodulators used to treat COVID-19 alongside steroids remains to be confirmed.

the lungs, and ICU admission.[2–4] Elevation of circulating GM-CSF in patients with emerging hyperinflammation 4 days after symptom onset differentiated mild or moderate from severe disease.[2] Since GM-CSF is produced by activated T cells in tissue microenvironments and is bound by extracellular matrix and GM-CSF receptors, its detection in the serum probably indicates elevated tissue levels. GM-CSF might therefore be an important target to treat early stages of the hyperinflammatory immune response and prevent its downstream sequelae.

Lenzilumab is a novel anti-human GM-CSF monoclonal antibody (Humaneered, Burlingame, CA, USA; manufactured by Calalent in the USA) that directly binds GM-CSF, with high specificity and affinity, and a slow off-rate, to prevent signalling through its receptor.[5] It has shown efficacy in clinical studies (NCT01603277, NCT02546284) of various disease settings with no serious adverse events attributed to its administration (Humanigen, unpublished). In a matched case-cohort study of patients admitted to hospital with COVID-19 pneumonia, lenzilumab was associated with a significantly shorter time to clinical improvement and a lower incidence of invasive mechanical ventilation (IMV) or death compared with the cohort receiving standard of care (8% *vs* 41%; p=0·07).[6]

The LIVE-AIR phase 3 randomised, double-blind, placebo-controlled clinical trial was designed to evaluate whether early intervention with lenzilumab, in patients hospitalised with COVID-19 who require supplemental oxygen but have not yet progressed to IMV, improves the likelihood of survival without ventilation beyond that provided by available treatments including corticosteroids or remdesivir.

Methods

Study design

This randomised, double-blind, placebo-controlled, phase 3 trial enrolled patients who were hospitalised with COVID-19 pneumonia from 29 sites in the USA and Brazil, with 85% of patients enrolled from US sites (appendix p 2). The study was done in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation E6 and the principles of the Declaration of Helsinki. The trial protocol was approved by the central or local institutional review board or ethics committee at each site. Patients—or their legally appointed representative—signed written informed consent forms. An independent data and safety monitoring board (DSMB) examined the safety and efficacy of the study medication compared with placebo in addition to standard of care throughout the duration of the study.

Participants

Patients eligible for enrolment were aged at least 18 years and gave informed consent (or provided consent via an authorised proxy, if necessary). SARS-CoV-2 infection was virologically confirmed, and pneumonia was diagnosed by chest x-ray or CT scan. Patients must have been hospitalised with a clinical ordinal score of 4 or 5 (oxygen saturation [SpO_2] ≤94% on room air or in need of supplemental oxygen in the form of low-flow oxygen, or both; adapted from the NIH-sponsored Adaptive COVID-19 Treatment Trial [ACTT], NCT04280705[7]) or clinical ordinal score of 3 (high-flow oxygen or non-invasive positive pressure ventilation [NPPV]).

Patients were excluded if they required IMV or extracorporeal membrane oxygenation (ECMO), were

pregnant or, in the view of the treating investigator, were not expected to survive the following 48 h from the time of randomisation. Patients with a confirmed diagnosis of bacterial pneumonia or other active or uncontrolled fungal or viral infection other than SARS-CoV-2 were also excluded. Women of childbearing potential were eligible if they had a negative urine or serum pregnancy test at screening–baseline and agreed to adequate contraception following their last dose of study drug. No limitations were placed on laboratory findings, hepatic or renal function, or presence of multiple organ system failure.

Randomisation and masking

Enrolled patients were randomly assigned 1:1 to receive lenzilumab or matched placebo in addition to standard treatment per institutional guidelines at each site. Patients were stratified at randomisation by age (≤65 *vs* >65 years) and disease severity (severe, SpO_2 ≤94% on room air or requiring low-flow supplemental oxygen; critical, requirement for high-flow oxygen delivery device or NPPV, or multi-organ dysfunction–failure or shock). A block randomisation method implemented with a central randomisation system (Rave Randomisation & Trial Supply Management; Medidata, NY, USA) was used to assign patients to treatment groups. Allocation of treatment was concealed to all investigators, study personnel, and patients. The investigational pharmacist was responsible for the preparation of study drug for each patient and was unmasked to the randomisation assignment.

Procedures

Following screening and baseline measures, lenzilumab or matching placebo (0·9% saline for injection) were administered by intravenous infusions beginning at day 0 within 12 h of randomisation in addition to standard care, in accordance with local site treatment guidelines and practice. All patients were monitored at screening, at baseline just before administration of study drug on day 0, and at least daily while hospitalised to day 28. All primary and key secondary endpoints were assessed by day 28. Three doses of lenzilumab (600 mg each) or placebo were administered 8 h apart via a 1-h intravenous infusion per dose. This regimen was selected to achieve serum levels of lenzilumab greater than 50 µg/mL, 1000-times higher than the estimated lung tissue levels of 0·05 µg/mL[9] required to achieve 50% neutralisation of GM-CSF activity in in-vitro preclinical models.[9] Parcetamol 500–1000 mg orally or intravenously and diphenhydramine 12·5–25 mg intravenously or 25 mg orally (or equivalent) were administered approximately 1 h before lenzilumab or placebo infusion to prevent hypersensitivity reactions.

Allowed treatments, at baseline and throughout the study, included all existing COVID-19 treatments: corticosteroids; convalescent plasma; remdesivir; or hydroxychloroquine with or without azithromycin. Previous treatment with FDA-approved monoclonal antibodies targeting IL-6 or IL-1, Janus kinase inhibitors, and SARS-CoV-2 neutralising monoclonal antibodies was allowed only if used more than 8 weeks before randomisation. Other investigational therapies to treat COVID-19 were not permitted.

Physical examinations including vital signs, assessment of COVID-19 pneumonia, ARDS assessment, use of supplemental oxygen, clinical status assessment, and pharmacokinetic and cytokine samples were done daily from baseline (day 0) to day 10, then on days 14 and 28 or at discharge. Laboratory assessment including blood chemistry and coagulation parameters were done on days 0, 1, 2, 4, 7, 10, 14, and 28 or at discharge. These measures are not presented herein. Adverse events were graded by means of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Serum for lenzilumab levels was collected at specific timepoints; pharmacokinetic analysis will be reported in a subsequent manuscript.

Outcomes

The primary efficacy endpoint was survival without ventilation (sometimes referred to as ventilator-free survival) by day 28. For the purposes of the survival analysis for the primary endpoint, an event was defined as mortality or the requirement for IMV. Survival without IMV is a robust composite endpoint used in many COVID-19 studies that is less prone to favour treatments with discordant effects on survival and days free of ventilation[10] and avoids the need for sample sizes approaching those of mortality trials to enable timely availability of study results.

An 8-point ordinal scale (from 1=death to 8=not hospitalised, no limitations) adapted from the NIH-sponsored ACTT study[7] was used for the assessment of clinical status. Time to recovery, a key secondary endpoint, was defined as the time to achieve an ordinal score of 6 (hospitalised, not requiring supplemental oxygen, and no longer requiring ongoing medical care), 7 (not hospitalised, limitation on activities, or requiring home oxygen), or 8 (not hospitalised and no limitations on activities) on the 8-point clinical status ordinal scale. Based on the Kaplan-Meier estimates, the recovery probabilities and associated 95% CIs on days 28 are reported. In addition, the 25th, 50th (median), and 75th percentiles of the time to recovery with associated 95% CIs are provided, as data permit. Other key secondary endpoints included the proportion of patients with the composite of IMV (ordinal score 2), ECMO (ordinal score 2), or death (ordinal score 1); ventilator-free days; duration of ICU stay; and mortality.

Additional secondary endpoints included time to two-point improvement (reported herein), proportion of patients who recovered, change in clinical status, incidence of severe ARDS, difference in mean haemophagocytic lymphohistiocytosis, duration of hospitalisation, time to discharge, proportion of

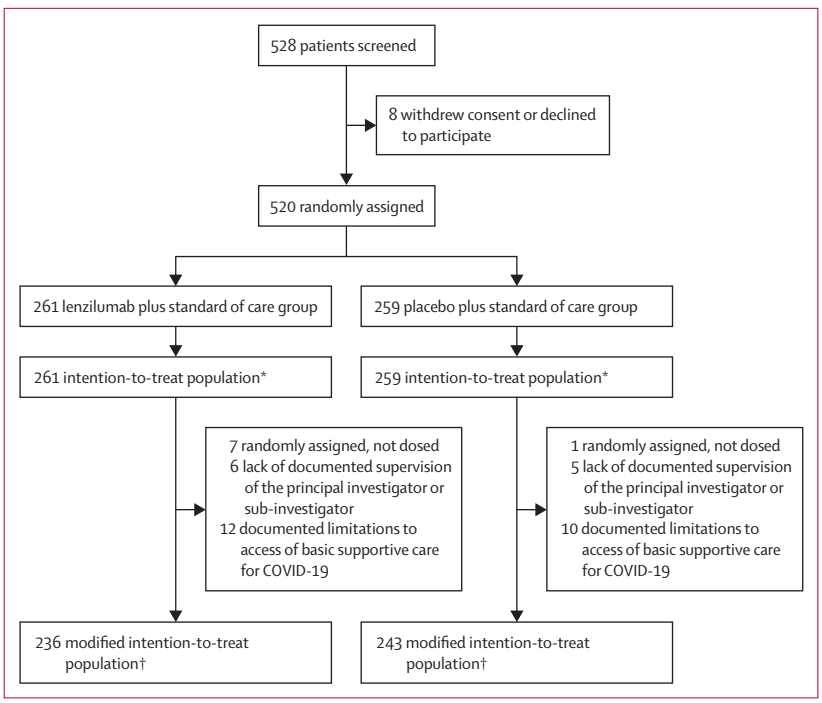

Figure 1: **Trial profile**
The intention-to-treat population consisted of all randomised patients. *The safety set included all patients who received at least one dose of study drug and is presented by the actual drug received; safety was assessed on study drug received, regardless of assignment group. Eight randomly assigned patients were never treated and were therefore excluded from the safety analysis but were included in the intention-to-treat analyses.†Randomly assigned patients who received at least one dose of study drug under the documented supervision of the principal investigator or sub-investigator were included in the modified intention-to-treat population. This population excluded patients from sites that had documented limitations in terms of access to basic supportive care for COVID-19. One patient, randomly assigned to placebo, received lenzilumab in error and was included in the safety analysis of lenzilumab and in the modified intention-to-treat efficacy analysis of placebo.

participants discharged from ICU and hospital, organ failure-free days, incidence of ICU stay, duration of high-flow oxygen, time to improvement in oxygenation, proportion of participants with improvement in oxygenation for 48 h, time to clinical improvement defined by National Early Warning Score 2 (NEWS2), proportion of participants with clinical improvement in NEWS2, and number of participants alive and off supplemental oxygen, all measured through day 28. These endpoints are not reported herein.

Statistical analysis

The original primary efficacy endpoint for this trial was the incidence of IMV or death up to day 28, which was then amended to time to recovery up to day 28. A prespecified interim analysis for safety, futility, and sample size re-estimation was performed by the DSMB when 50% of the events had occurred to assess the time to recovery in patients receiving standard treatment and whether any amendments to the protocol were required to validate the effect of lenzilumab in this patient population. The DSMB was masked to all other data. On the basis of the interim analysis, the sample size was increased to the approximately 515 participants who would be necessary to observe 402 recovery events. Several months after increasing the sample size of the trial, while maintaining masking by both the sponsor and the DSMB, the primary endpoint was modified to survival without IMV to day 28 on the basis of the changing therapeutic landscape, with an increased focus on mortality and IMV as more clinically meaningful and reliable study endpoints.

The sample size estimate was based on the event rates in similar patient populations from other published studies.[10–12] The event rate of patients who required IMV or died by day 28 in the placebo group was estimated as 25%, and the event rate in the lenzilumab treatment group was approximated as 15%, resulting in a hazard ratio (HR) of 0·565.[13] By means of a Cox proportional hazard model to test for inequality of the HR, a total of 100 events were calculated to provide 81% power to detect a difference with a two-sided alpha of 5% at the final analysis and assuming a fixed follow-up of 28 days. Therefore, approximately 516 enrolled patients (258 patients in each treatment group) were needed to observe the 100 targeted events.

The primary endpoint was the difference between lenzilumab treatment and placebo treatment in survival without IMV to 28 days following treatment in the prespecified, modified intention-to-treat population (mITT), in which patients received at least one dose of investigational treatment under the documented supervision of the principal investigator or sub-investigator. This population was used for the primary analysis, including a Cox proportional hazard model (HR lenzilumab relative to placebo) accounting for the stratification variables (ie, age and disease severity) and was supplemented by a display of Kaplan-Meier curves in each treatment group. The Cox proportional hazard model included the time to first event (death or IMV) as the dependent variable (1=IMV use or death, 0=alive with no IMV use), treatment (covariate), and strata (covariates). Where data were non-proportional on the basis of a χ^2 test proposed by Grambsch and Therneau with a global p value of <0·05, a Cox proportional hazard model with weighted extension was used to correct for non-proportionality. For sensitivity and exploratory analyses of the primary endpoint, stepwise addition of all possible two-way interactions between the three covariates was considered. The model with the best fit (lowest Akaike information criteria value) was selected. A further sensitivity analysis was done on the primary endpoint including the most common comorbidities (hypertension, obesity, diabetes), respiratory comorbidities (asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis) and baseline CRP as a marker of systemic inflammation as covariates, each assessed independently of other covariates. Patients who were alive and did not get placed on IMV were right censored at the date of the last non-missing assessment on or before day 28. The primary analysis was done in the mITT population and in the prespecified subgroup of patients

who received remdesivir or both remdesivir and any corticosteroid.

For each secondary endpoint, the proportion of patients who had had the event was calculated by treatment group. An odds ratio (OR) was calculated for the composite endpoint of the first incident IMV, ECMO, or death by means of logistic regression and including baseline age group and disease category as covariates. For ventilator-free days and duration of ICU stay, the ANCOVA model of normality assumption was found to be clearly violated (eg, p<0·05 for the Shapiro-Wilk test for normality), so a sensitivity analysis was done by means of an alternative non-parametric approach. A negative binomial regression model that was specified in the statistical analysis plan was used, although the data did not conform to a Pascal distribution. Given that the data are not a Pascal distribution, a non-parametric stratified Wilcoxon test was done. A zero inflated negative binomial regression was done on ventilator days as a sensitivity analysis. HRs were calculated for each of time to death and time to recovery, separately, as described in the aforementioned statistical analysis plan. For time to recovery, deaths were censored at day 28. Patients who were alive yet did not recover were right censored at the date of the last non-missing assessment on the 8-point clinical status ordinal scale on or before day 28. Last, the proportion of patients who had treatment-emergent serious adverse events that were National Cancer Institute Common Terminology Criteria for Adverse Events grade 3 or more were quantified for each randomisation group by system organ class. All data reported herein are reported to day 28. Due to the low amount of missing data, the last observation carried forward method was used. Robust monitoring yielded 100% source data verification and adherence to good clinical practices.

Analyses were performed using SAS for Windows statistical software, version 9.4 or higher, except where other software was deemed more appropriate. This trial is registered with ClinicalTrials.gov, NCT04351152.

Role of the funding source

The study sponsor funded all aspects of the study, participated in data collection, data analysis, data interpretation, and writing of the report and the decision to submit the manuscript for publication.

Results

Enrolment began with the first patient dosed on May 5, 2020, and ended with the last patient dosed on Jan 27, 2021. 528 patients were screened, of whom 520 were randomly assigned and included in the intention-to-treat (ITT) population (figure 1). 41 patients (8%) were excluded from the mITT population. Of these, 22 were from two sites in Brazil (12 in the lenzilumab group and ten in the placebo group) who joined during the final stage of the study and had documented limitations in terms of access to basic supportive COVID-19 care including high-flow oxygen devices, owing to the pandemic surge in Brazil, which resulted in a disproportionate increase from low-flow supplemental oxygen directly to IMV. Eight randomly assigned patients were not dosed, and 11 lacked documented supervision of dosing by either the principal investigator or sub-investigator. These participants were excluded while the study remained masked. The mITT population included

	Lenzilumab group (n=236)	Placebo group (n=243)	Total (n=479)
Sex			
Female	83 (35%)	85 (35%)	168 (35%)
Male	153 (65%)	158 (65%)	311 (65%)
Age (years)			
Mean	61 (14)	61 (14)	61 (14)
Median	62 (28–98)	62 (22–96)	62 (22–98)
<65	143 (61%)	142 (58%)	285 (59%)
≥65	93 (39%)	101 (42%)	194 (41%)
>80	19 (8%)	12 (5%)	31 (6%)
Body-mass index (kg/m²)			
Mean	33 (8)	32 (8)	33 (8)
≥30 kg/m²	136 (58%)	128 (53%)	265 (55%)
Race			
American Indian	4 (2%)	0	4 (1%)
Asian	10 (4%)	5 (2%)	15 (3%)
Black	38 (16%)	33 (14%)	71 (15%)
White	165 (70%)	178 (73%)	343 (72%)
Mixed	1 (<1%)	0	1 (<1%)
Other	18 (8%)	27 (11%)	45 (9%)
Ethnicity			
Hispanic or Latinx	83 (35%)	102 (42%)	185 (39%)
Not Hispanic or Latinx	151 (64%)	138 (57%)	289 (60%)
Not reported	2 (1%)	2 (1%)	4 (1%)
Region			
USA	203 (86%)	207 (85%)	410 (86%)
Brazil	33 (14%)	36 (15%)	69 (14%)
Supplemental oxygen			
Room air (clinical ordinal score=5)	24 (10%)	17 (7%)	41 (9%)
Low-flow oxygen (clinical ordinal score=4)	120 (51%)	121 (50%)	241 (50%)
High-flow oxygen or non-invasive positive pressure ventilation (clinical ordinal score=3)	92 (39%)	105 (43%)	197 (41%)
C-reactive protein (mg/L)			
Mean	100 (80)	96 (71)	98 (76)
Median	77 (40–145)	82 (41–125)	79 (41–137)
Comorbidity (%)			
Cardiovascular			
Hypertension	146 (62%)	168 (69%)	314 (66%)
Congestive heart failure	31 (13%)	25 (10%)	56 (12%)
Coronary artery disease	35 (15%)	30 (12%)	65 (14%)
Diabetes	120 (51%)	136 (56%)	256 (53%)
Chronic liver disease	10 (4%)	14 (6%)	24 (5%)

(Table 1 continues on next page)

	Lenzilumab (n=236)	Placebo (n=243)	Total (n=479)
(Continued from previous page)			
Chronic kidney disease	33 (14%)	34 (14%)	67 (14%)
Respiratory			
Asthma	32 (14%)	19 (8%)	51 (11%)
Interstitial pulmonary fibrosis	3 (1%)	1 (<1%)	4 (1%)
Chronic obstructive pulmonary disease	18 (8%)	17 (7%)	35 (7%)
Treatments (%)			
Remdesivir	170 (72%)	177 (73%)	347 (72%)
Corticosteroids	221 (94%)	228 (94%)	449 (94%)
Remdesivir and corticosteroids	163 (69%)	168 (69%)	331 (69%)

Data are n (%), mean (SD), or median (IQR).

Table 1: **Baseline characteristics of the modified intention-to-treat population**

	Lenzilumab group (n=236)	Placebo group (n=243)	Lenzilumab *vs* placebo hazard ratio or odds ratio (95% CI)	p value
Survival without ventilation to day 28	198 (84%; 79–89)	190 (78%; 72–83)	1·54† (1·02–2·32)	0·040
Incidence of invasive mechanical ventilation, extracorporeal membrane oxygenation, or death	35 (15%; 11–21)	51 (21%; 16–27)	0·67‡ (0·41–1·10)	0·11
Ventilator-free days§¶	25‖ (8·8)	23‖ (10·5)	..	0·077‖
ICU stay¶ (days)	6‖ (10)	7‖ (11)	..	0·16
Invasive mechanical ventilation	26 (11%; 8–16) **	49 (20%; 16–26) **	0·52† (0·32–0·82)	0·0059
Mortality	24 (10%; 6–14)**	34 (14%; 10–19)**	0·72† (0·42–1·23)	0·24
Time to recovery (median number of days per quartile)				
25%	5 (4–5)	5 (5–5)	..	0·43
50%	8 (7–9)	8 (7–9)	..	..
75%	15 (11–20)	19 (13–NA)	..	..

Data are n (%; 95% CI), median (IQR), or mean (SD) unless stated otherwise. Analysis of the modified intention-to-treat population. Survival without ventilation by day 28 was analysed using Kaplan-Meier estimates; secondary outcomes are presented using Kaplan-Meier estimates or estimated marginal mean. *All data censored at 28 days following enrolment. †Cox proportional hazard model for time to event with age (≤65, >65 years) and severity (severe or critical) strata as covariates. ‡Odds ratio with age (≤65, >65 years) and severity (severe or critical) strata as covariates. §See appendix (p 7) for additional analyses. ¶See appendix (p 8) for additional analyses. ‖Stratified Wilcoxon p value with age (≤65, >65 years) and severity (severe, critical) strata as covariates. **Kaplan-Meier estimates for proportion of patients. NA=not possible to estimate.

Table 2: **Primary and key secondary endpoints***

236 (90%) patients randomly assigned to lenzilumab and 243 (94%) patients randomly assigned to placebo. In the mITT population, 11 patients (five in the lenzilumab group and six in the placebo group) were lost to follow-up: seven had ecovered and were discharged and subsequently lost to follow-up, and four patients withdrew from the study before day 28 (two lenzilumab and two placebo).

Baseline characteristics were similar between the groups (table 1). Approximately two-thirds of the patients were male, and mean age of participants was 61 years. The patients were of diverse racial and ethnic backgrounds, with 185 (39%) of them self-reported as Hispanic or Latinx and 72 (15%) reported as Black or African American, which is consistent with real-world demographics of hospitalised patients with COVID-19. At baseline, 197 (41%) patients had ordinal score 3 (high-flow oxygen or NPPV), 241 (50%) had ordinal score 4 (low-flow supplemental oxygen) and 41 (9%) had ordinal score 5 (SpO_2 ≤94% on room air) on the adapted 8-point clinical ordinal scale. Hypertension was the most common comorbidity, followed by obesity, diabetes, chronic kidney disease, and coronary artery disease. 449 (94%) patients received corticosteroids, 347 (72%) received remdesivir, and 331 (69%) received both, while also receiving placebo or lenzilumab. Baseline demographics of patients receiving remdesivir were similar between the study groups (appendix p 3) and were not different from those reported in the mITT population. Given that 331 (69%) of patients given remdesivir were also given steroids, the demographics for that group are assumed to be similar and are not reported. Patients were hospitalised for a median of 2 days (IQR for lenzilumab 1–5 and for placebo 1–4) before random assignment.

The study achieved its prespecified primary endpoint. Treatment with lenzilumab was associated with a greater likelihood of achieving survival without IMV to day 28 compared with the placebo group (HR 1·54; 95% CI 1·02–2·32; p=0·040; table 2, figure 2). The estimate of survival without IMV, through day 28 was 198 (84%; 95% CI 79–89) in patients treated with lenzilumab and 190 (78%; 72–83) in patients treated with placebo (table 2, figure 2A). Relative to patients receiving placebo, the likelihood of survival without IMV was statistically greater in the prespecified subgroups of patients receiving lenzilumab in addition toremdesivir, steroids, or remdesivir and steroids (appendix p 4). 15 patients in each group received no steroids, did not progress to IMV or death, and therefore were not analysable for the purposes of this subgroup analysis. No statistical interaction was identified between lenzilumab and remdesivir (HR 0·39; 95% CI 0·14–1·09; p=0·073) or lenzilumab and concomitant remdesivir and steroids (HR 0·39; 0·14–1·08; p=0·070).

The ITT population was evaluated as a sensitivity analysis (table 3). For the primary outcome, lenzilumab was associated with a statistically greater likelihood of survival without IMV to day 28 compared with placebo (HR 1·90; 95% CI 1·03–3·49; p=0·043). In the prespecified lenzilumab treated subgroups receiving remdesivir or remdesivir and corticosteroids, the ITT sensitivity analysis showed statistically greater likelihood of survival without IMV relative to subgroups treated with placebo. Given the similarity of the survival without IMV improvement in the primary analysis for patients who received steroids, which was 449 patients (94% of all patients), this information is not further reported for sensitivity analyses. Further sensitivity analyses of the primary endpoint, including univariate analyses of

baseline factors that might influence the primary analysis of survival without IMV, and a sensitivity analysis by means of various baseline comorbidities, respiratory conditions, and CRP as a marker of systemic inflammation as covariates, were done (see appendix pp 6–7, 11). These analyses showed that CRP levels less than the median value of 79 mg/L exhibited the greatest likelihood of achieving survival without IMV with the lowest p value.

With respect to secondary outcomes, the occurrence of the composite outcome of IMV, ECMO, or death, the number of ventilator-free days, the length of ICU stay, and mortality were unaffected by lenzilumab treatment in the overall population (table 2). In a subgroup analysis of concomitant treatment, the composite of IMV, ECMO, or death occurred in 26 (Kaplan-Meier estimate 13%) of 170 patients treated with lenzilumab and 45 (Kaplan-Meier estimate 23%) of 177 patients treated with placebo who were also treated with remdesivir (OR 0·51; 95% CI 0·29–0·89; nominal p=0·020) or remdesivir and corticosteroids (26 [Kaplan-Meier estimate 14%] of 163 *vs* 45 [Kaplan-Meier estimate 27%] of 168; 0·51; 0·28–0·89; nominal p=0·018, respectively; appendix p 4). IMV was used in 26 (11%) patients treated with lenzilumab and 49 (20%) patients treated with placebo in the overall population (OR 0·52; 95% CI 0·32–0·82; nominal p=0·0059; table 2). In patients treated with concomitant remdesivir, 19 (11%) of 170 treated with lenzilumab and 42 (24%) of 177 treated with placebo underwent IMV (OR 0·39; 95% CI 0·23–0·67; nominal p=0·0007; appendix p 4); and in those treated with concomitant remdesivir and steroids, 20 (12%) of 163 treated with lenzilumab and 42 (25%) of 168 treated with placebo underwent IMV (0·39; 0·23–0·67; nominal p=0·0007; appendix pp 4–5). Relative to placebo, ventilator-free days were 2·7 days fewer (incidence rate ratio 0·51; 95% CI 0·29–0·90; nominal p=0·019) with lenzilumab and concomitant remdesivir as well as 3·0 days fewer (0·50; 0·29–0·89; p=0·018) with lenzilumab, remdesivir, and corticosteroids (appendix p 8). The greatest differences in ventilator days (0 *vs* 15 days) and ICU days (7 *vs* 16 days) observed with lenzilumab compared with placebo were in the highest quartile of duration (appendix p 9). Other secondary outcomes, including mortality, time to recovery, and time to two-point improvement did not achieve significance in the overall population or in those treated with remdesivir or remdesivir and steroids (table 2, appendix pp 4–5, 10, 12, 14).

Of 520 randomly assigned patients, 8 were never treated and were therefore excluded from the safety analysis. One patient, randomly assigned to placebo,

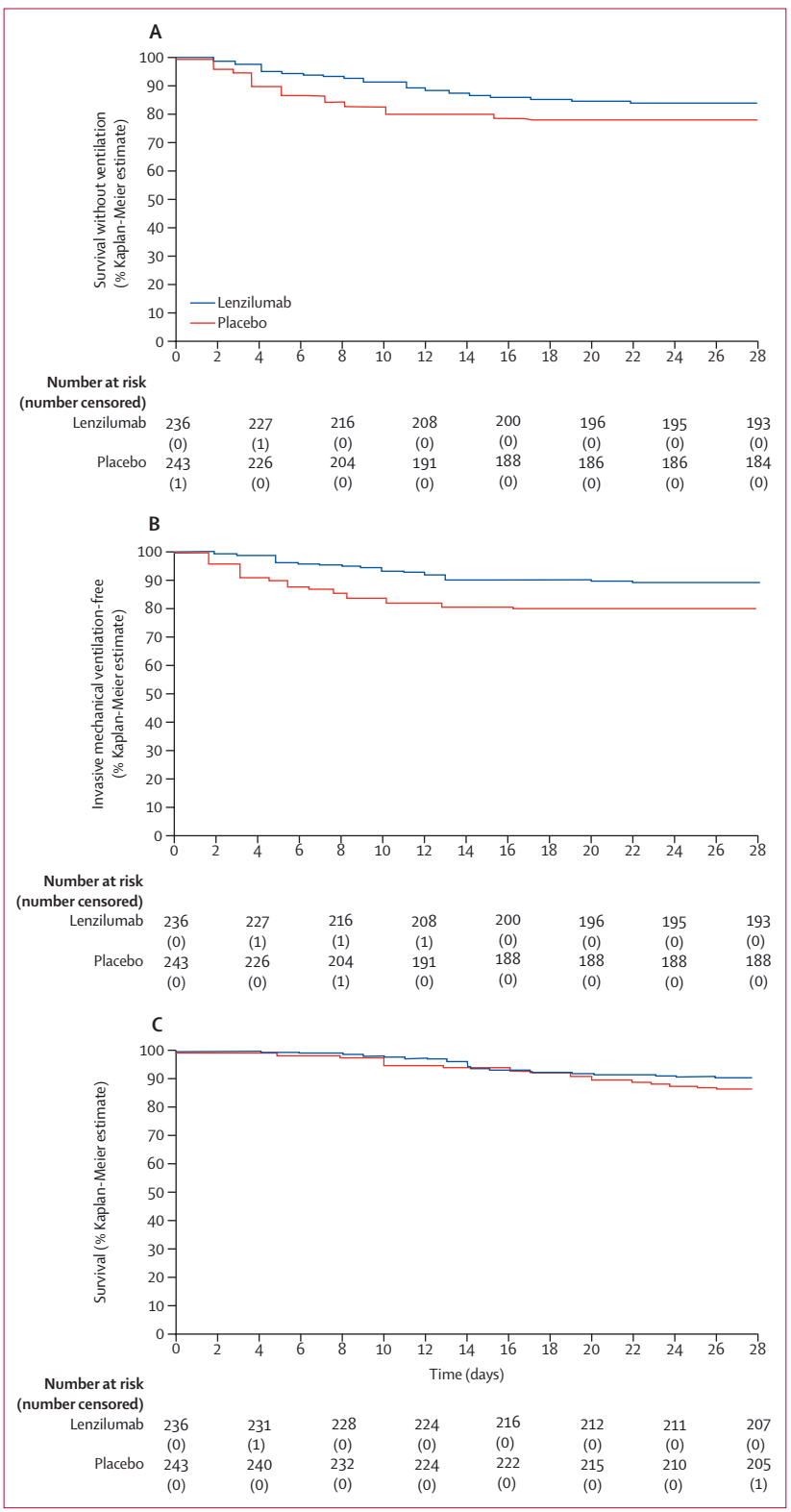

Figure 2: **Kaplan-Meier plot of survival without invasive mechanical ventilation and its individual components**

(A) Plot for survival without invasive mechanical ventilation in the mITT population. The mITT analysis was the primary efficacy analysis. Separation of the survival curves occurred as early as 3 days following treatment. Following day 10, separation was maintained for the duration of the observation period. (B) Plot for invasive mechanical ventilation. (C) Plot for mortality. mITT=modified intention-to-treat.

	Kaplan-Meier estimate of survival without ventilation		Lenzilumab *vs* placebo hazard ratio† (95% CI)	p value
	Lenzilumab group‡ (95% CI)	Placebo group‡ (95% CI)		
Overall§ (n=520; 261 lenzilumab, 259 placebo)	191 (81%; 76–86)	197 (76%; 71–81)	1·90 (1·03–3·49)	0·043
Remdesivir (n=354; lenzilumab 175, placebo 179)	145 (83%; 76–89)	132 (74%; 66–79)	1·81 (1·15–2·84)	0·0099
Remdesivir and steroids (n=338; lenzilumab 168, placebo 170)	138 (82%; 76–87)	122 (72%; 65–78)	1·82 (1·16–2·86)	0·0092

Analysis of the intention-to-treat population.*All data censored at 28 days following enrolment. †Cox proportional hazard model for time to event with age (≤65, >65 years) and severity (severe or critical) strata as covariates. ‡Number of patients and Kaplan-Meier estimates for proportion of patients presented with 95% CI. §Primary endpoint.

Table 3: **Sensitivity analyses of primary endpoint in the intention-to-treat population***

	Lenzilumab (n=255)	Placebo (n=257)	Total (n=512)
Any adverse event ≥grade 3	68 (27%)	84 (33%)	152 (30%)
Respiratory, thoracic, and mediastinal disorders			
Total	64 (25%)	71 (28%)	135 (26%)
Respiratory failure	24 (9%)	31 (12%)	55 (11%)
Acute respiratory failure	18 (7%)	22 (9%)	40 (8%)
Hypoxia	15 (6%)	15 (6%)	30 (6%)
Pulmonary embolism	5 (2%)	3 (1%)	8 (2%)
Acute respiratory distress syndrome	4 (2%)	3 (1%)	7 (1%)
Cardiac disorders			
Total	15 (6%)	14 (5%)	29 (6%)
Cardiac arrest	8 (3%)	4 (2%)	12 (2%)
Cardiorespiratory arrest	3 (1%)	4 (2%)	7 (1%)
Acute myocardial infarction	0	3 (1%)	3 (1%)
Infections and infestations			
Total	10 (4%)	16 (6%)	26 (5%)
Septic shock	5 (2%)	9 (4%)	14 (3%)
Sepsis	2 (1%)	5 (2%)	7 (1%)
Pneumonia bacterial	0	6 (2%)	6 (1%)
Vascular disorders			
Total	10 (4%)	15 (6)	25 (5%)
Shock	3 (1%)	6 (2%)	9 (2%)
Hypotension	2 (1%)	5 (2%)	7 (1%)
Renal and urinary disorders			
Total	5 (2%)	11 (4%)	16 (3%)
Acute kidney injury	5 (2%)	8 (3%)	13 (3%)
General disorders and administration site conditions			
Total	4 (2%)	11 (4%)	15 (3%)
Multiple organ dysfunction syndrome	3 (1%)	6 (2%)	9 (2%)

Data are n (%). Patients could experience more than one subcategory event.

Table 4: **Most common grade 3 and higher adverse events (overall prevalence ≥1·0%)**

received lenzilumab in error and was included in the safety analysis of lenzilumab. Adverse events of grade 3 and higher were reported in 68 (27%) of 255 patients treated with lenzilumab and 84 (33%) of 257 patients treated with placebo (table 4). Serious adverse events were reported in 64 (25%) patients treated with lenzilumab and 77 (30%) patients treated with placebo. The overall incidence of cardiac disorders was similar between treatment groups, lenzilumab (15 [6%]) and placebo (14 [5%]). Eight (3%) patients treated with lenzilumab and four (2%) patients treated with placebo had cardiac arrest. Cardiorespiratory arrest occurred in three (1%) patients treated with lenzilumab and four (2%) patients treated with placebo. No patient treated with lenzilumab and three (1%) patients treated with placebo had acute myocardial infarction. Cardiac arrest, cardiorespiratory arrest, and acute myocardial infarction were 4% for both lenzilumab (n=11) and placebo (n=11). Lenzilumab, compared with placebo, produced no infusion-related reactions, no attributable serious adverse events, no reports of pulmonary alveolar proteinosis, and no increased incidence of infection. No deaths were ascribed to adverse events.

Discussion

The results of this randomised trial indicate that lenzilumab improves survival without ventilation in adults hospitalised with COVID-19 pneumonia. A reduction in the risk of IMV was also observed. Importantly, the observed benefit was greater than that provided by standard background care including remdesivir and corticosteroids. Improvement in ventilator-free days and incidence of IMV, ECMO, or death with lenzilumab treatment was not observed in the primary analysis population but was observed in the prespecified remdesivir treated subgroups. Lenzilumab was well tolerated with no significant differences in adverse events or serious adverse events compared with placebo. No differences in secondary infection rates were observed with lenzilumab treatment. The potential for pulmonary alveolar proteinosis, a concern with anti-GM-CSF therapeutics, has not been reported with lenzilumab in this or other clinical trials.[6,14–16]

Targeting the hyperinflammatory immune response induced by SARS-CoV-2 viral infection has been evaluated with anti-cytokine therapies in multiple clinical trials of COVID-19 with some success. Although early reports evaluating IL-6 inhibition were inconsistent,[17–19] more recent open-label studies have suggested a role for tocilizumab in certain patient populations.[11,20] On the basis of the REMAP-CAP[21] and RECOVERY[11] studies, tocilizumab is recommended for patients who are within 24 h of ICU admission and require either IMV, high-flow oxygen, non-invasive ventilation, or are experiencing rapidly increasing oxygen demands and have significantly increased markers of inflammation (CRP >75 mg/L).[21]

In contrast to REMAP-CAP and RECOVERY, where median baseline CRP levels were 136 mg/L and 143 mg/L,

respectively, LIVE-AIR participants had a median baseline CRP of 79 mg/L (appendix p 11). These exploratory findings might indicate the therapeutic potential of targeting a single upstream cytokine earlier in the disease process, guided by baseline CRP. The concept is supported by the SAVE-MORE trial, in which soluble urokinase plasminogen activator receptor (suPAR) serum levels, predictive of risk of respiratory failure in COVID-19, were successfully used to guide treatment with an IL-1α–β inhibitor (anakinra) for improved World Health Organization Clinical Progression Scale, Sequential Organ Failure Assessment, and 28-day mortality.[22] Further evaluation of CRP for guiding treatment with lenzilumab might be warranted.

In contrast to lenzilumab, two other anti-GM-CSF monoclonal antibodies are undergoing evaluation for their safety and efficacy in the treatment of COVID-19. Mavrilimumab is a monoclonal antibody that binds to the α subunit of the GM-CSF receptor. Although an initial single-centre, prospective cohort study of 13 non-mechanically ventilated patients who received mavrilimumab (a single 6 mg/kg intravenous infusion) and 26 control patients appeared promising,[23] a subsequent double-blind, randomised trial of mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation was terminated early, did not meet its primary endpoint of proportion of patients free of supplemental oxygen support at day 14, and exhibited no significant improvements in clinical outcomes.[24] A study of mavrilimumab in 116 patients with COVID-19 requiring supplemental oxygen therapy without mechanical ventilation—a similar population to that of LIVE-AIR—showed a reduced requirement of mechanical ventilation and improved survival through day 29.[25]

Otilimab, another anti-GM-CSF monoclonal antibody, has been evaluated in a double-blind, randomised, placebo-controlled study that enrolled 806 adults who required high-flow oxygen, non-invasive ventilation, or IMV—a different population from that recruited for LIVE-AIR. In the overall population, otilimab (a single 90 mg infusion) did not confer a significant improvement in the primary outcome of proportion of patients alive and free of respiratory failure at day 28, although a post-hoc analysis suggested benefit in those aged 70 years and older.[26]

Several potential reasons might explain inconsistencies in observed outcomes of studies with anti-GM-CSF agents. One factor might be related to the unique pharmacological properties of lenzilumab, including differences in binding affinity, dosage, or dissociation rate between lenzilumab and the other two anti-GM-CSF monoclonal antibodies. The clinical population in LIVE-AIR reflects an earlier stage of disease progression than was studied with otilimab and suggests that GM-CSF inhibition alone might be more beneficial earlier in the disease process. Other relevant differences might include patient selection; dose limitations with otilimab and mavrilimumab, or the manner (over 24 h) in which lenzilumab was administered might also be factors.

A strength of this study was adequate power to show a significant difference for a clinically meaningful outcome across multiple sensitivity analyses. Secondary endpoints of ventilator-free days, duration of ICU stay, composite of IMV–ECMO–death, and mortality were not significantly different, but provide point estimates supportive of the primary efficacy results. An additional strength is that lenzilumab was administered in addition to available treatments including corticosteroids and remdesivir in the majority of patients. The study contributes to the emerging body of evidence about how CRP concentrations relate to the pathogenesis of COVID-19 and to patient and treatment selection, which warrants further investigation. These points are further addressed in the prospectively designed ACTIV-5–BET-B (NCT04583969) trial, which includes lenzilumab treatment and will use CRP to define the primary analysis population.

Among study limitations, LIVE-AIR was not designed to show a survival benefit. However, survival without IMV, which has been used in other studies such as EMPACTA[19] as the primary endpoint and RECOVERY[13] as a secondary endpoint, was used herein as a composite endpoint including mortality. Another limitation is heterogeneity in the availability of and access to basic supportive care and remdesivir across countries. Additionally, the exclusion of IL-6 or Janus kinase inhibitors might not be reflective of current practice; however, approximately 60% of LIVE-AIR patients were on room air or low-flow oxygen support for which the use of tocilizumab or baricitinib is not recommended. In this context, LIVE-AIR raises the possibility that lenzilumab might be positioned for use before ICU admission and progression of respiratory failure requiring high-flow oxygen and non-invasive or invasive ventilation.

In summary, LIVE-AIR showed that lenzilumab treatment of hospitalised patients with COVID-19 can improve the likelihood of survival without the need for mechanical ventilation, with a safety profile similar to that of placebo.

Contributors

OA, DC, GC, and CD had access to the raw data. ZT and CDB contributed to the study design, data collection, data review, interpretation, writing and approval of the manuscript, and the decision to submit. JB, CP, CRL, CFK, and RO contributed to the data collection, data review, interpretation, writing and approval of the manuscript, and the decision to submit. VCM contributed to the study design, data collection, data analysis, data review, interpretation, writing and approval of the manuscript, and the decision to submit. VMC accessed and verified the data, and contributed to the data analysis, data review, interpretation, writing and approval of the manuscript, and the decision to submit. WSA contributed to the study design, data analysis, data review, interpretation, writing and approval of the manuscript, and the decision to submit. CD, DC, and OA contributed to the study design and data analysis, verified the data, and contributed to the interpretation, writing and approval of the manuscript, and the decision to submit. GC contributed to the data analysis, data review, interpretation, writing and approval of the manuscript, and the decision

to submit. ADB contributed to the study design, data collection, data analysis, data review, interpretation, writing and approval of the manuscript, and the decision to submit. ZT had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Individual participant data including data dictionaries will not be made available.

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