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Effect of Canakinumab vs Placebo on Survival Without Invasive Mechanical Ventilation in Patients Hospitalized With Severe COVID-19
A Randomized Clinical Trial

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IMPORTANCE Effective treatments for patients with severe COVID-19 are needed.

OBJECTIVE To evaluate the efficacy of canakinumab, an anti–interleukin-1β antibody, in patients hospitalized with severe COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This randomized, double-blind, placebo-controlled phase 3 trial was conducted at 39 hospitals in Europe and the United States. A total of 454 hospitalized patients with COVID-19 pneumonia, hypoxia (not requiring invasive mechanical ventilation [IMV]), and systemic hyperinflammation defined by increased blood concentrations of C-reactive protein or ferritin were enrolled between April 30 and August 17, 2020, with the last assessment of the primary end point on September 22, 2020.

INTERVENTION Patients were randomly assigned 1:1 to receive a single intravenous infusion of canakinumab (450 mg for body weight of 40-<60 kg, 600 mg for 60-80 kg, and 750 mg for >80 kg; n = 227) or placebo (n = 227).

MAIN OUTCOMES AND MEASURES The primary outcome was survival without IMV from day 3 to day 29. Secondary outcomes were COVID-19–related mortality, measurements of biomarkers of systemic hyperinflammation, and safety evaluations.

RESULTS Among 454 patients who were randomized (median age, 59 years; 187 women [41.2%]), 417 (91.9%) completed day 29 of the trial. Between days 3 and 29, 198 of 223 patients (88.8%) survived without requiring IMV in the canakinumab group and 191 of 223 (85.7%) in the placebo group, with a rate difference of 3.1% (95% CI, −3.1% to 9.3%) and an odds ratio of 1.39 (95% CI, 0.76 to 2.54; *P* = .29). COVID-19–related mortality occurred in 11 of 223 patients (4.9%) in the canakinumab group vs 16 of 222 (7.2%) in the placebo group, with a rate difference of −2.3% (95% CI, −6.7% to 2.2%) and an odds ratio of 0.67 (95% CI, 0.30 to 1.50). Serious adverse events were observed in 36 of 225 patients (16%) treated with canakinumab vs 46 of 223 (20.6%) who received placebo.

CONCLUSIONS AND RELEVANCE Among patients hospitalized with severe COVID-19, treatment with canakinumab, compared with placebo, did not significantly increase the likelihood of survival without IMV at day 29.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04362813

Visual Abstract

Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 272

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COVID-19 is caused by infection with SARS-CoV-2. A subgroup of infected patients develop viral pneumonia and experience respiratory failure, which in some cases progresses to acute respiratory distress syndrome.[1,2] Most critically ill patients require invasive mechanical ventilation (IMV), and mortality in this group is high.[2,3] Patients with severe COVID-19 often present with systemic hyperinflammation associated with excessive cytokine release and high serum levels of inflammatory proteins such as C-reactive protein (CRP), ferritin, and D-dimer.[1,4-8] Dexamethasone, a glucocorticoid with broad anti-inflammatory action, has improved outcomes of patients with severe COVID-19.[9] More recently, preliminary results of the RECOVERY trial, a platform study with large patient populations, have shown that in patients hospitalized with COVID-19, hypoxia, and systemic inflammation, the IL-6 inhibitor tocilizumab improved survival and other clinical outcomes.[10]

IL-1β is an upstream proinflammatory cytokine that is involved in the pathogenesis of a variety of autoinflammatory conditions and induces the production of secondary inflammatory mediators, including IL-6.[11] In vitro experiments have shown that infection with SARS-CoV-2 triggers activation of the inflammasome and the maturation and release of IL-1β.[12] Post mortem examination of lungs of patients who died of COVID-19 pneumonia have revealed intense inflammasome formation.[13] Immunoprofile studies have shown that IL-1β is one of the inflammatory cytokines that defines the "core COVID-19 signature."[4]

The CAN-COVID trial was a phase 3 randomized clinical trial conducted to evaluate the efficacy of canakinumab in patients hospitalized with severe COVID-19.

Key Points

Question Is the anti–interleukin-1β antibody canakinumab effective to treat patients hospitalized with COVID-19 and hyperinflammation?

Finding This randomized clinical trial included 454 patients hospitalized with severe COVID-19 not requiring invasive mechanical ventilation (IMV) and with elevated C-reactive protein or ferritin levels. Treatment with intravenous canakinumab vs placebo resulted in survival without IMV at 29 days of 88.8% vs 85.7%, a difference that was not statistically significant.

Meaning Among patients hospitalized with severe COVID-19, treatment with canakinumab, compared with placebo, did not significantly increase the likelihood of survival without IMV.

Methods

Trial Design and Oversight

This randomized, double-blind, placebo-controlled phase 3 trial was conducted at 39 hospitals in Europe and the United States with varying standard care treatment approaches both regionally and over the course of the pandemic. The ethics committee of each site provided approval. Participating patients provided written informed consent. An independent safety monitoring committee provided oversight. The study protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively.

In the double-blind phase 3 CAN-COVID trial, patients hospitalized with severe COVID-19 were randomly assigned in a 1:1 ratio to receive 1 dose of canakinumab or placebo. In addition, all patients continued to receive standard care treatment for COVID-19 per local practice.

Efficacy and monitoring of adverse events (AEs) were performed daily, and laboratory assessments every other day until day 29 and on days 57 and 127, in hospitalized patients. For patients who had been discharged from the hospital, follow-up visits conducted by telephone were scheduled at days 15, 29, 57, and 127.

Herein we report results of the interim analyses performed after all patients completed day 29, when the primary and secondary end points were analyzed.

Patients

Eligible participants were hospitalized patients with severe COVID-19, at least 12 years old (United States) or 18 years old (Europe), and had hypoxemia but did not require IMV. Inclusion criteria included a diagnosis of infection with SARS-CoV-2 within 7 days prior to randomization, diagnosis of pneumonia with pulmonary infiltrates on chest x-ray or computed tomographic scan within 5 days prior to randomization, peripheral capillary oxygen saturation of 93% or less on room air or arterial oxygen partial pressure/fraction of inspired oxygen less than 300 mm Hg, and blood levels of CRP of 20 mg/L or greater or ferritin of 600 µg/L or greater. Patients were not eligible if they had been treated with therapies targeting IL-1 or IL-6, had a suspected or known untreated active infection due to another pathogen, or if progression to death was imminent within 24 hours according to the investigator.

Randomization

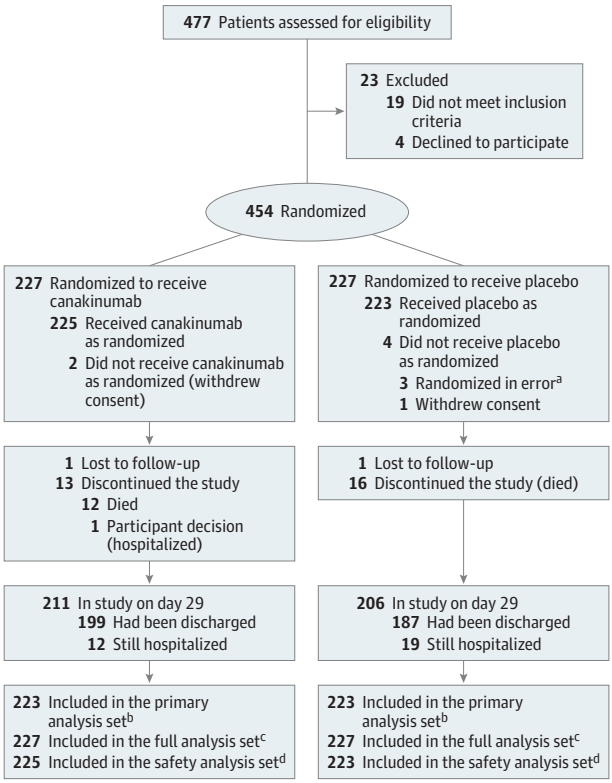
The randomization was stratified by country, with a block size of 4 within each stratum. It was implemented using an interactive response technology system in which a new patient meeting the inclusion and exclusion criteria was randomly assigned to a treatment group based on a random allocation sequence. This sequence was created by a separate randomization office of the sponsor and kept blinded to the study team until the scheduled unblinding for data analysis.

Interventions

Randomized patients received a single dose of canakinumab (450 mg for body weight of 40-<60 kg, 600 mg for 60-80 kg, and 750 mg for >80 kg) or placebo in 250 mL of 5% dextrose infused intravenously over 2 hours. The study therapy was prepared by an unblinded pharmacist independent of the study team to maintain the blind. After dilution, canakinumab and placebo preparations were indistinguishable.

Use of glucocorticoids, convalescent serum or plasma, antivirals, and anticoagulants was permitted during the trial. Per protocol, immunomodulatory therapies, such as biologic agents targeting IL-1 or IL-6, or tumor necrosis factor were prohibited.

Figure 1. Patient Disposition and Outcomes



[a] These 3 patients were randomized in error because they did not meet all of the eligibility criteria.

[b] The primary analysis set included randomized patients who received canakinumab or placebo and had at least 1 assessment of clinical status between days 3 and 29.

[c] The full analysis set included all randomized patients.

[d] The safety analysis set included all patients who received canakinumab or placebo.

Outcomes

The clinical status of patients was assessed using the World Health Organization's (WHO) 9-point ordinal scale.[14] Based on this assessment, the primary end point was the proportion of patients who survived without ever requiring IMV from day 3 to day 29 (inclusive). A patient was defined as a nonresponder if the worst clinical status at any time from day 3 (inclusive) up to day 29 (inclusive) was category 6, 7, or 8 on the WHO 9-point ordinary scale, corresponding to requiring IMV or death. Day 3 was used as the initial day of assessment due to the potential rapid deterioration of patients' clinical status with natural SARS-CoV-2 infection. Patients who discontinued the study or were lost to follow-up before day 29 were considered responders if they did not require IMV at any time after day 3 and fulfilled 1 of 2 conditions: discharged from the hospital with a clinical status of 0 or 1 on the WHO 9-point ordinal scale or the last assessment of clinical status occurred at day 15 or later and was better than at baseline.

The key secondary outcome was the proportion of patients who died of COVID-19 (causality assessed by investigators) between days 1 and 29. Other secondary outcomes were the ratio to baseline in serologic biomarkers reflecting systemic hyperinflammation (CRP, ferritin, and D-dimer levels) and safety evaluations based on the analysis of AEs until day 29. Supplemental and sensitivity analyses on the primary and secondary efficacy end points are described in eAppendix 1 in Supplement 3. Three predefined exploratory analyses on the primary end point included the number of patients who met the nonresponder criteria for the primary end point or used any prohibited anti-IL-1 or anti-IL-6 medications during the study from day 1 up to day 29, the primary end point response by subgroups (see complete list of subgroups in eAppendix 2 of Supplement 3), and time to use of IMV or death up to day 29.

Other predefined exploratory outcomes included time to death, change in clinical status from day 1 to day 29 using the WHO 9-point ordinal scale and during hospitalization, time to treatment response such as discharge from hospital, duration for in-hospital outcomes such as in the intensive care unit, duration receiving therapy with supplementary oxygen, duration receiving IMV, and change in the American Association for Transplantation and Cellular Therapy grade for cytokine release syndrome over time, which was calculated based on hypotension and hypoxia.[15] Pharmacokinetic, pharmacodynamic, and biomarker analyses will be evaluated after study completion and are not reported in this article.

Sample Size

Based on the literature available at the time of study design, the IMV-free survival rate in the target hospitalized population was assumed to be in the range from 20% to 50%.

With a 1:1 randomization ratio and 2-sided type I error control at .05, a sample size of 450 patients was calculated to provide at least 89% power for the primary analysis to detect a difference of at least 15% in the rate of survival without requiring IMV. This difference was defined as the minimum clinically meaningful benefit of interest.

Statistical Analysis

Efficacy analyses were performed using the full analysis set comprising all randomized patients according to the treatment assigned by randomization. Safety analyses were performed using the safety data set including data from all participants who received study treatment.

Analysis of the primary efficacy end point included randomized patients who received study treatment and who had at least 1 assessment of clinical status between days 3 and 29. Patients who died or discontinued from the study before day 3 were excluded from the primary analysis but were included in a supplementary analysis on the primary end point. The proportions of patients in the canakinumab and placebo groups who survived by day 29 without using IMV anytime from day 3 to day 29 were compared based on their odds ratio (OR)—which was estimated using a logistic regression model on the logit of probability for survival without the need for IMV with study treatment as main effect—and adjusted by region (United States, Europe) and baseline clinical status (≤4, ≥5) on the WHO 9-point ordinal scale. A patient who discontinued early from the study or was lost to

Table 1. Demographic, Clinical, and Laboratory Baseline Characteristics[a]

Characteristic	No. (%)[b] Canakinumab (n = 227)	Placebo (n = 227)
Age, median (IQR), y	59 (49-69)	57 (50-68)
Age >65 y	78 (34)	72 (32)
Sex		
Male	135 (59)	132 (58)
Female	92 (41)	95 (42)
Race/ethnicity, No./total (%)		
White	159/208 (76)	156/215 (73)
Black or African American	35/208 (17)	37/215 (17)
Asian	10/208 (5)	9/215 (4)
American Indian or Alaska Native	3/208 (1)	8/215 (4)
Native Hawaiian or other Pacific Islander	1/208 (0.5)	5/215 (2)
Hispanic or Latino	70/224 (31)	66/220 (29)
Country or region		
United States	126 (56)	127 (56)
Russia	76 (34)	77 (34)
Western Europe	25 (11)	23 (10)
Weight, median (IQR), kg	86 (75-99)	87 (76-99)
BMI[c]		
No.	227	222
Median (IQR)	29.9 (26.5-34.8)	30.8 (27.0-34.7)
BMI >30.0, No./total (%)[c]	112/227 (49)	125/222 (55)
Comorbidities		
Hypertension	120 (53)	133 (59)
Diabetes	79 (35)	85 (37)
Chronic cardiac disease	48 (21)	44 (19)
Chronic kidney disease	23 (10)	17 (7.5)
Chronic obstructive pulmonary disease	20 (8.8)	13 (5.7)
Asthma	18 (7.9)	17 (7.5)
Cerebrovascular disease	10 (4.4)	17 (7.5)
Time from symptom onset to randomization, median (IQR), d	9 (7-12)	9 (6-12)
Time from diagnosis to randomization, median (IQR), d	2 (1-5)	2 (1-4)
ASTCT CRS grade[d]		
Grade 1: least sick	19 (8.4)	18 (7.9)
Grade 2	152 (67)	154 (68)
Grade 3	49 (22)	45 (20)
Grade 4: sickest	7 (3.1)	6 (2.6)
PaO_2/FiO_2, median (IQR)	180.1 (112.3-261.9)	179.6 (127.5-268.8)
SARS-CoV-2 viral load by nasopharyngeal swab, No./total (%)		
≥500 copies/mL	124/182 (68.1)	126/175 (72.0)
<500 copies/mL	58/182 (31.9)	49/175 (28.0)
Serum biomarkers of inflammation		
C-reactive protein, median (IQR), mg/L	89 (47-153)	77 (42-136)
Ferritin, median (IQR), µg/L	681 (304-1271)	631 (305-1160)
D-dimer, median (IQR), µg/L FEU	980 (540-1894)	958 (612-1406)
Medication initiated prior to day 1		
Heparin (any dose)	165 (73)	165 (73)
Dexamethasone ≥6 mg/d[e]	92 (41)	73 (32)
Azithromycin	85 (37)	85 (37)
Remdesivir	49 (22)	45 (20)
Hydroxychloroquine	31 (14)	29 (13)
Convalescent plasma or serum	8 (3.5)	8 (3.5)

Abbreviations: ASTCT, American Society for Transplantation and Cellular Therapy; BMI, body mass index; CRS, cytokine release syndrome; FEU, fibrinogen equivalent units; IQR, interquartile range; Pao_2/Fio_2, ratio of arterial oxygen partial pressure/fraction of inspired oxygen; WHO, World Health Organization.

[a] Baseline measurements were performed prerandomization per protocol. Proportions of patients with each clinical status according to the WHO 9-point ordinal scale at baseline are provided in Figure 3.

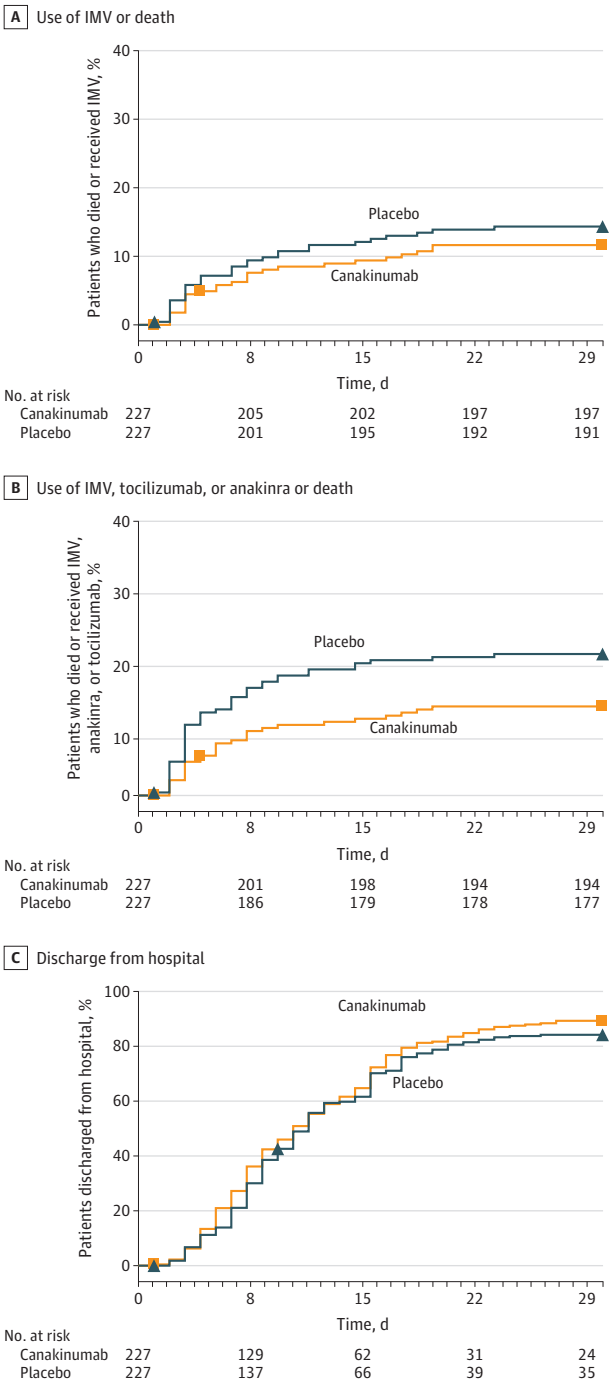
[b] Unless otherwise specified.

[c] BMI is calculated as weight in kilograms divided by height in meters squared.

[d] ASTCT CRS grade was calculated as described based on hypotension and hypoxia with increased intervention associated with increased grading score.[17] Grade 1 indicates no hypotension/hypoxia; grade 2, no vasopressors/low-flow nasal cannula; grade 3, vasopressor/high-flow nasal cannula, face mask, nonrebreather mask, or Venturi mask; and grade 4, multiple vasopressors/positive pressure oxygenation.

[e] Dexamethasone ≥6 mg/d or equivalent glucocorticoid.

Figure 2. Use of IMV or Death and Discharge From Hospital



Kaplan-Meier estimates are for patients with COVID-19 and hyperinflammation (N = 454, 227 in each group) treated with the standard care plus 1 single dose of canakinumab or placebo on day 1. Data markers represent censoring times. A and B, Patients were censored after day 29 or at the last follow-up if they discontinued the study; C, patients who died were not censored up to day 29. By day 29, 12 patients died in the canakinumab group and 16 in the placebo group. Most patients completed the observation period of 29 days, and therefore the median observation time was 29 days. Of note, 14 patients were readmitted to the hospital after discharge: 8 in the canakinumab group and 6 in the placebo group. The median time to hospital discharge was 10 days (95% CI, 9-12) for the canakinumab group and 11 days (95% CI, 10-12) for the placebo group.

follow-up before day 29 was considered as a responder if they did not require IMV any time after day 2 and either was discharged from hospital with clinical status lower than 2 or the patient's last clinical status was obtained after day 14 and was better than at baseline. Otherwise, the patient was considered as a nonresponder. A supplementary analysis was performed in which all patients who were lost to follow-up or discontinued the study before day 29 with a clinical status higher than 1 were considered as nonresponders. As a sensitivity analysis, the difference in the rates of IMV-free survival between treatment groups was estimated using a marginal standardization method in which the rate difference was derived from the predicted rates for every patient using a logistic regression model, with treatment as main effect of interest adjusted by region and baseline clinical status.[16]

The same logistic regression model for the primary analysis was used for the key secondary end point of death related to COVID-19 during the 29-day period after study treatment and for the exploratory end point of IMV-free survival without use of anakinra or tocilizumab.

The hypothesis tests for primary and key secondary analyses were conducted in hierarchical order with the 2-sided family-wise type I error rate controlled at 0.05, which was also the threshold for statistical significance. No other secondary, exploratory, or supplementary analyses presented were included as part of the testing hierarchy that controlled for multiplicity. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

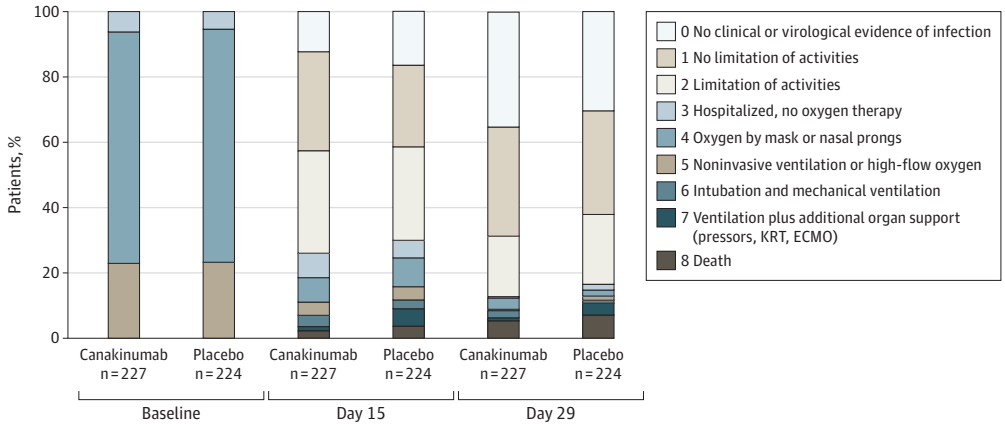
Time to death or use of IMV, time to death, and use of IMV or of anakinra or tocilizumab were evaluated using survival analysis. Survival curves were elaborated based on Kaplan-Meier estimates of survival functions, and the hazard ratios were obtained using a Cox proportional hazard model. Survival curves were visually examined to confirm that there were no apparent violations of the proportional hazard assumption. The exploratory end points of time to discharge from hospital, time to recovery, and time to improvement of at least 2 levels in clinical status up to day 29 were analyzed based on Cox-proportional hazards model adjusted by region and baseline clinical status. Baseline demographic and clinical characteristics of the patients, the evolution of serum levels of markers of inflammation, and other exploratory outcomes were summarized and presented using descriptive statistics. SAS software version 9.4 (SAS Institute Inc) was used for the analysis of this study.

Results

Trial Population

From 477 patients screened from April to August 2020, 454 adult patients hospitalized with severe COVID-19 were enrolled and randomized (**Figure 1**). Six randomized patients discontinued the study before receiving study drug: 3 withdrew their consent to participate immediately after randomization and 3 did not meet eligibility criteria. In total, 448 patients received canakinumab (n = 225) or placebo (n = 223).

Figure 3. Evolution of Clinical Status Over Time



Patient state	Score	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Uninfected	0	0	0	28 (12.3)	37 (16.5)	80 (35.2)	68 (30.4)
Ambulatory, not in hospital, or in hospital and ready for discharge	1	0	0	69 (30.4)	56 (25.0)	76 (33.5)	71 (31.7)
	2	0	0	71 (31.3)	64 (28.6)	42 (18.5)	48 (21.4)
Hospitalized, mild disease	3	14 (6.2)	12 (5.4)	17 (7.5)	12 (5.4)	1 (0.4)	4 (1.8)
	4	161 (70.9)	160 (71.4)	17 (7.5)	20 (8.9)	8 (3.5)	4 (1.8)
Hospitalized, severe disease	5	52 (22.9)	52 (23.2)	9 (4.0)	9 (4.0)	1 (0.4)	3 (1.3)
	6	0	0	8 (3.5)	6 (2.7)	5 (2.2)	2 (0.9)
	7	0	0	3 (1.3)	12 (5.4)	2 (0.9)	8 (3.6)
Dead	8	0	0	5 (2.2)	8 (3.6)	12 (5.3)	16 (7.1)

The graphics and table present the clinical status according to the World Health Organization's 9-point ordinal scale at baseline and days 15 and 29 of patients with COVID-19 and hyperinflammation (full analysis set, N = 454, which includes 3 patients in the placebo arm who were misrandomized and had no assessments available) treated with the standard care as per local practice plus 1 single dose of canakinumab or placebo on day 1. In the table, n is the number of patients with assessment of clinical status performed at each visit, with last observation carried forward imputation for missing data at days 15 and 29, and No. is the number of patients with a given score at each visit. Percentages were calculated as No./n × 100. ECMO indicates extracorporeal membrane oxygenation; and KRT, kidney replacement therapy.

There were no notable differences in demographics or baseline disease characteristics between the canakinumab and placebo groups (**Table 1**). The median age was 59 years, with one-third of patients aged older than 65 years, and approximately half were obese (body mass index >30 [calculated as weight in kilograms divided by height in meters squared]). Biomarkers of inflammation were elevated, and most patients (70%) were receiving low-flow oxygen by mask or nasal prongs.

The number of patients treated with dexamethasone (≥6 mg/d) or equivalent prior to day 1 was 92 of 227 (41%) in the canakinumab group and 73 of 227 (32%) in the placebo group (Table 1).

By day 29, 12 patients treated with canakinumab died, 1 decided to discontinue the study, and 1 was lost to follow-up. Further, 16 who received placebo died and 1 was lost to follow-up (Figure 1).

Concomitant anti-inflammatory or COVID-19–related treatments initiated on or after day 1 are reported in eTable 1 in Supplement 3. Dexamethasone (≥6 mg/d) or equivalent was given to 33 of 227 patients (14.5%) in the canakinumab group vs 51 of 227 (22.5%) in the placebo group, and convalescent plasma or serum was given to 15 of 227 (6.6%) in the canakinumab group vs 30 of 227 (13.2%) in the placebo group. Per protocol, tocilizumab and anakinra were prohibited; however, tocilizumab was administered to 5 of 227 patients (2.2%) in the canakinumab group vs 20 of 227 (8.8%) in the placebo group, and 2 patients in the canakinumab group and 1 in the placebo group received anakinra.

Efficacy

Primary Outcome

The proportion of patients who survived without requiring IMV from day 3 to day 29 was 198 of 223 (88.8%) in the canakinumab group and 191 of 223 (85.7%) in the placebo group, with a rate difference of 3.1% (95% CI, −3.1% to 9.3%) and an OR of 1.39 (95% CI, 0.76 to 2.54; P = .29). Kaplan-Meier curves for survival without IMV are shown in **Figure 2**. Predefined sensitivity and supplementary analyses on the primary end point supported these results (eAppendix 1 in Supplement 3).

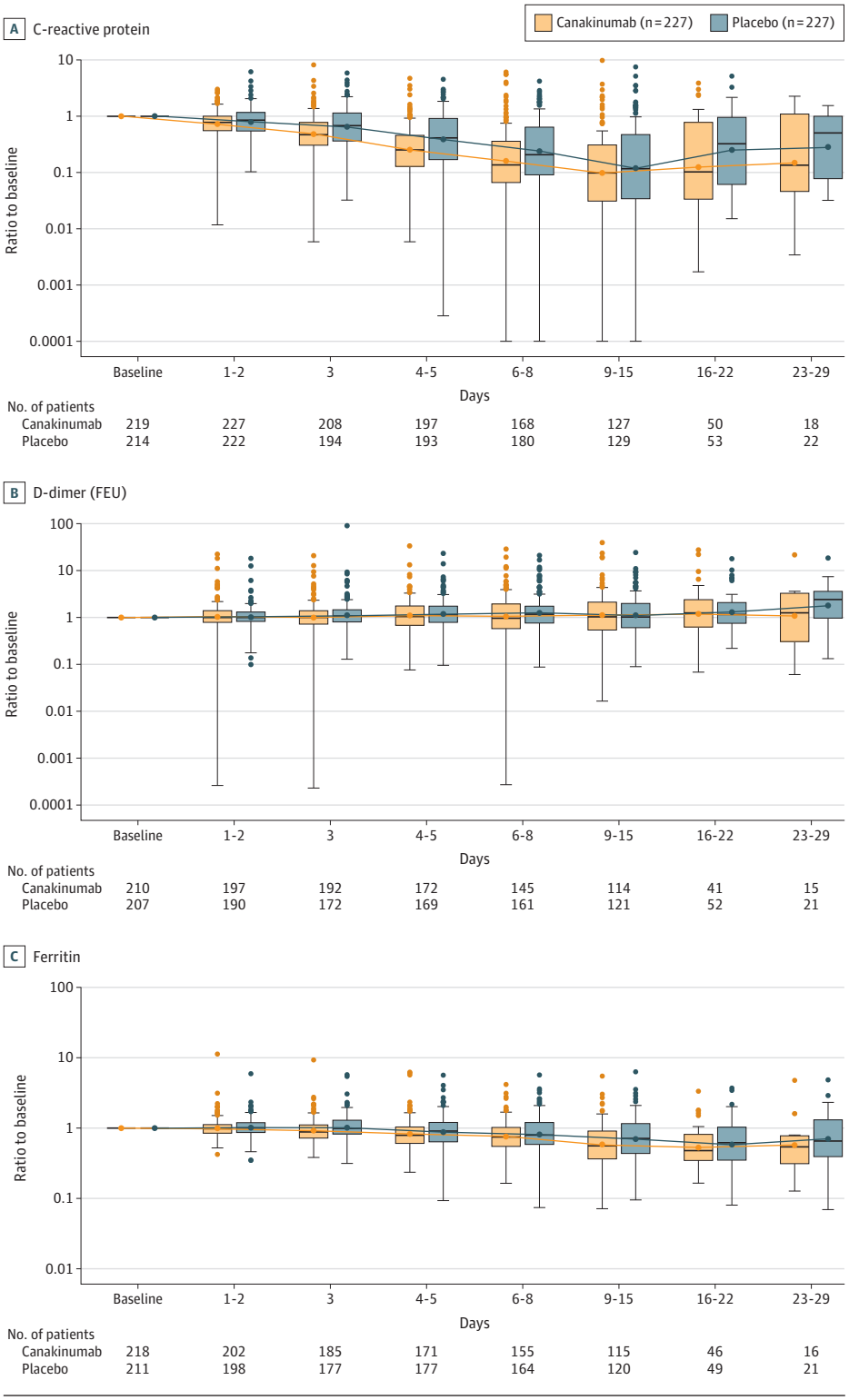
Secondary Outcome

The proportion of patients with COVID-19–related death by day 29 was 11 of 223 (4.9%) in the canakinumab group vs 16 of 222 (7.2%) in the placebo group, with a rate difference of −2.3% (95% CI, −6.7% to 2.2%) and an OR of 0.67 (95% CI, 0.30 to 1.50). A predefined supplementary analysis supported these results (eAppendix 1 in Supplement 3).

Predefined Exploratory Outcomes

Although biologic drugs targeting IL-1 or IL-6 were prohibited during the trial per protocol, some patients were treated with tocilizumab or anakinra (eTable 1 in Supplement 3).

Figure 4. Blood Concentrations of Inflammatory Markers Over Time



Plots present ratios to baseline of blood concentrations of C-reactive protein (A), D-dimer (B), and ferritin (C) from baseline until day 29, using logarithmic scales. Boxes represent interquartile ranges (IQRs); horizontal lines in the boxes indicate median values, with whiskers indicating 1.5 × IQR below the first quartile and above the third quartile; and dots outside the boxes are potential outliers. Dots in the boxes, which are linked by lines between time points, represent geometric means. For each time interval, only 1 value per patient is presented; if there was more than 1 value available, the value obtained at a time closer to the midpoint of the interval was selected. Results were obtained in the full analysis set, the number of patients with measurements available at each time point for the placebo and canakinumab groups are presented in the table under the graphic. FEU indicates fibrinogen equivalent units.

Results of an exploratory analysis showed that 195 of 223 patients (87.4%) in the canakinumab group vs 177 of 223 (79.4%) in the placebo group survived without ever requiring IMV or receiving anakinra or tocilizumab by day 29, with an OR of 1.93 (95% CI, 1.12 to 3.31) and a rate difference of 8.1% (95% CI, 1.2% to 14.9%) (Figure 2).

Table 2. Summary of Adverse Events[a]

Category	Patients, No. (%)	
	Canakinumab (n = 225)	Placebo (n = 223)
Any AE	122 (54.2)	120 (53.8)
Most common AEs (≥3%)		
Acute respiratory failure	13 (5.8)	14 (6.3)
Leukocytosis	11 (4.9)	8 (3.6)
Hypokalemia	10 (4.4)	4 (1.8)
Hypoxia	9 (4.0)	11 (4.9)
Constipation	9 (4.0)	10 (4.5)
C-reactive protein increased	9 (4.0)	7 (3.1)
Pyrexia	9 (4.0)	2 (0.9)
Anemia	8 (3.6)	8 (3.6)
Acute respiratory distress syndrome	7 (3.1)	4 (1.8)
Hypoproteinemia	6 (2.7)	7 (3.1)
Pneumonia	6 (2.7)	7 (3.1)
Hyperglycemia	3 (1.3)	9 (4.0)
Acute kidney injury	3 (1.3)	8 (3.6)
Infections[b]	23 (10.2)	43 (19.3)
Treatment-related AEs	11 (4.9)	9 (4.0)
SAEs	36 (16.0)	46 (20.6)
Serious infections[b]	11 (4.9)	21 (9.4)
Treatment-related SAEs	0	1 (0.4)
AEs with outcome of death (all cause)[c]	17 (7.6)	21 (9.4)
AEs requiring discontinuation of study drug	1 (0.4)[d]	0
AEs requiring additional therapy	83 (36.9)	92 (41.3)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

[a] The table reflects AEs observed until day 29 in the safety population. A patient with multiple AEs was counted only once for each category.

[b] MedDRA System Organ Class of infections and infestations.

[c] AEs occurred until day 29, but deaths attributed to them could occur after day 29.

[d] Due to erythema.

The clinical status of patients at baseline and days 15 and 29 using the WHO 9-point ordinal scale is presented in **Figure 3**. Most patients were receiving oxygen therapy by mask or nasal prongs at baseline. By day 29, 80 of 227 patients (35.2%) in the canakinumab group vs 68 of 224 (30.4%) in the placebo group had no clinical or virologic evidence of infection (clinical status of 0). On day 29, the proportion of patients with clinical status of 5 to 8 (ie, patients who needed noninvasive mechanical ventilation, high-flow oxygen, or IMV or who died) was 20 of 227 (8.8%) in the canakinumab group vs 29 of 224 (13%) in the placebo group. The proportion of patients remaining hospitalized on day 29 was 12 of 227 (5.3%) in the canakinumab group vs 19 of 227 (8.4%) in the placebo group. No significant differences in the rate of hospital discharge over time were observed between the 2 groups (Figure 2). Additional predefined exploratory efficacy outcomes are reported in eAppendix 2 and the eFigure in Supplement 3.

Serum Concentrations of Inflammatory Markers Over Time

CRP, ferritin, and D-dimer levels over time in patients treated with canakinumab and placebo are shown in **Figure 4**.

Adverse Events

The rate of AEs observed in the canakinumab and placebo groups are shown in **Table 2**. Most AEs until day 29 were considered to be related to the underlying condition and not related to study drug.

Administration of study drug was discontinued in 1 patient who experienced erythema during canakinumab infusion, resolving 1 day later. AEs of infections and infestations were numerically less frequent in the canakinumab group than in the placebo group. Serious AEs were observed in 36 of 225 patients (16%) treated with canakinumab vs 46 of 223 (20.6%) who received placebo. Fatal AEs (COVID-19–related or not related) with onset before day 29 occurred in 17 of 225 patients (7.6%) in the canakinumab group vs 21 of 223 (9.4%) in the placebo group. Four additional patients experienced AEs after day 29 that led to death before the data cutoff date for the database lock: 3 in the canakinumab group and 1 in the placebo group; none were considered related to study drug. All AEs observed in more than 1 patient are listed in eTable 3 in Supplement 3.

Discussion

In this multicenter, double-blind, placebo-controlled, randomized clinical trial conducted at 39 hospitals in Europe and the United States, the IL-1β inhibitor canakinumab did not significantly increase the likelihood of survival without IMV among patients hospitalized with severe COVID-19. These findings were also consistent for the secondary outcome of COVID-19–related mortality.

The study was initiated based on the premise that IL-1 inhibition had previously been shown to inhibit inflammatory

response in patients with systemic hyperinflammation and cytokine storm in conditions such as macrophage activation syndrome, possibly due to the inhibition of downstream mediators, including IL-6.[11] It was, therefore, hypothesized that IL-1 inhibition would decrease the release of cytokines in patients with severe COVID-19 pneumonia.

Early during the pandemic and at the time of study design, the results of case-control studies with the IL-1 blocker anakinra further supported this hypothesis. However, more recently, a randomized trial with anakinra was stopped early because of the observed lack of efficacy in decreasing the need for IMV or death.[18-25] At the time of study design, there were limited data available to estimate the rate of disease progression after hospital admission for patients with COVID-19. Based on the early literature, the IMV-free survival rate in the target population was considered most likely in the range from 20% to 50%.[1,26,27] A difference of 15% in the primary end point was defined as the minimum clinically meaningful benefit of interest at the time of protocol development early in the pandemic. However, observed event rates in the study were 11.2% and 14.3% in the canakinumab and placebo groups, respectively. Because a 15% difference was not achievable, the results should be interpreted based on the observed effect size and confidence interval.

Strict criteria for selecting patients with COVID-19 and systemic hyperinflammation were not available at the time that this study was designed and conducted. These criteria continue to be refined.[28] The AE rates were numerically similar for the canakinumab and placebo groups.

Limitations

This study had several limitations. First, the standard care for treatment of COVID-19 evolved during the conduct of the trial. In terms of glucocorticoids, prior to study therapy, more patients in the canakinumab group had received dexamethasone (or equivalent), but this imbalance was reversed after study therapy was administered when more patients receiving placebo initiated dexamethasone (or equivalent) than those in the canakinumab group. Second, there was an imbalance in the use of the prohibited medications (tocilizumab and anakinra) after study therapy was initiated; these medications were not defined as rescue therapies per protocol. Third, throughout the course of the pandemic, the mortality and morbidity outcomes continued to become increasingly more favorable, likely due to a better understanding of the disease and its management (ie, standard care treatment).[1-3] These challenges underscore the difficulty in conducting randomized clinical trials in the changing treatment approach during the COVID-19 pandemic. These shortcomings may be best addressed in the future by event-driven trial designs.

Conclusions

Among patients hospitalized with severe COVID-19, treatment with canakinumab, compared with placebo, did not significantly increase the likelihood of survival without IMV at day 29.

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