

## ORIGINAL ARTICLE

# Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A.S. Foulkes, N.K. Horick, B.C. Healy, R. Shah, A.M. Bensaci, A.E. Woolley, S. Nikiforow, N. Lin, M. Sagar, H. Schrager, D.S. Huckins, M. Axelrod, M.D. Pincus, J. Fleisher, C.A. Sacks, M. Dougan, C.M. North, Y.-D. Halvorsen, T.K. Thurber, Z. Dagher, A. Scherer, R.S. Wallwork, A.Y. Kim, S. Schoenfeld, P. Sen, T.G. Neilan, C.A. Perugino, S.H. Unizony, D.S. Collier, M.A. Matza, J.M. Vinh, K.A. Bowman, E. Meyerowitz, A. Zafar, Z.D. Drobni, M.B. Bolster, M. Kohler, K.M. D'Silva, J. Dau, M.M. Lockwood, C. Cubbison, B.N. Weber, and M.K. Mansour, for the BACC Bay Tocilizumab Trial Investigators\*

## ABSTRACT

**BACKGROUND**

The efficacy of interleukin-6 receptor blockade in hospitalized patients with coronavirus disease 2019 (Covid-19) who are not receiving mechanical ventilation is unclear.

**METHODS**

We performed a randomized, double-blind, placebo-controlled trial involving patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hyperinflammatory states, and at least two of the following signs: fever (body temperature  $>38^{\circ}\text{C}$ ), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%. Patients were randomly assigned in a 2:1 ratio to receive standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight) or placebo. The primary outcome was intubation or death, assessed in a time-to-event analysis. The secondary efficacy outcomes were clinical worsening and discontinuation of supplemental oxygen among patients who had been receiving it at baseline, both assessed in time-to-event analyses.

**RESULTS**

We enrolled 243 patients; 141 (58%) were men, and 102 (42%) were women. The median age was 59.8 years (range, 21.7 to 85.4), and 45% of the patients were Hispanic or Latino. The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81;  $P=0.64$ ), and the hazard ratio for disease worsening was 1.11 (95% CI, 0.59 to 2.10;  $P=0.73$ ). At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had had worsening of disease. The median time to discontinuation of supplemental oxygen was 5.0 days (95% CI, 3.8 to 7.6) in the tocilizumab group and 4.9 days (95% CI, 3.8 to 7.8) in the placebo group ( $P=0.69$ ). At 14 days, 24.6% of the patients in the tocilizumab group and 21.2% of the patients in the placebo group were still receiving supplemental oxygen. Patients who received tocilizumab had fewer serious infections than patients who received placebo.

**CONCLUSIONS**

Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19. Some benefit or harm cannot be ruled out, however, because the confidence intervals for efficacy comparisons were wide. (Funded by Genentech; ClinicalTrials.gov number, NCT04356937.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Stone at the Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, 55 Fruit St., Boston, MA 02114, or at [jhstone@mgh.harvard.edu](mailto:jhstone@mgh.harvard.edu).

\*A complete list of the BACC Bay Tocilizumab Trial investigators and members of the data and safety monitoring board is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

This article was published on October 21, 2020, at [NEJM.org](http://NEJM.org).

DOI: 10.1056/NEJMoa2028836

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**I**NFECTIONS WITH SEVERE ACUTE RESPIRATORY syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), now number more than 7 million in the United States.<sup>1</sup> At the peak of the pandemic to date, more than 1000 Americans died from Covid-19 each day, and more than 214,000 had died as of October 13, 2020. After an incubation period, the acute viral phase in patients with symptomatic Covid-19 usually manifests as influenza-like symptoms. In some persons, the illness progresses to hypoxemic respiratory failure.<sup>2,3</sup> Evidence suggests that the pathophysiological basis of this profound decline is a severe inflammatory response resembling cytokine release syndrome.<sup>4,5</sup> In this phase, patients have markedly abnormal inflammatory markers, including elevated serum interleukin-6, ferritin, and C-reactive protein levels.<sup>6-9</sup> Higher concentrations of interleukin-6 in serum are associated with higher levels of SARS-CoV-2 viremia,<sup>10</sup> prolonged viral RNA shedding,<sup>11</sup> progression to mechanical ventilation,<sup>12</sup> and death.<sup>13</sup> These findings led us to hypothesize that interleukin-6 receptor blockade might interrupt this inflammatory cascade at a crucial stage.

Evidence from nonrandomized trials and open-label studies has been contradictory,<sup>14-33</sup> and published results from randomized, double-blind, placebo-controlled trials have been lacking. We performed the investigator-initiated Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial, a randomized, double-blind, placebo-controlled trial of tocilizumab administered relatively early in the disease course, with the aim of preventing progression of Covid-19. We hypothesized that early intervention with interleukin-6 receptor blockade might limit progression to hypoxemic respiratory failure or death, reduce the risk of clinical worsening, and decrease the duration of supplemental oxygen use.

## METHODS

### TRIAL DESIGN

We conducted the trial at seven Boston hospitals. The trial was approved by the Mass General Brigham institutional review board and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent in keeping with institutional guidelines. The in-

vestigators designed the trial, collected the data, and performed the analysis. Genentech funded the trial and provided tocilizumab but had no role in data analysis, data interpretation, or writing of the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. The trial was overseen by a data and safety monitoring board. All the authors participated in writing the manuscript that was submitted. No one who is not an author contributed to writing the manuscript.

### PATIENTS

Patients were eligible for enrollment if they were 19 to 85 years of age and had SARS-CoV-2 infection confirmed by either nasopharyngeal swab polymerase chain reaction or serum IgM antibody assay. Patients had to have at least two of the following signs: fever (body temperature  $>38^{\circ}\text{C}$ ) within 72 hours before enrollment, pulmonary infiltrates, or a need for supplemental oxygen in order to maintain an oxygen saturation higher than 92%. At least one of the following laboratory criteria also had to be fulfilled: a C-reactive protein level higher than 50 mg per liter, a ferritin level higher than 500 ng per milliliter, a D-dimer level higher than 1000 ng per milliliter, or a lactate dehydrogenase level higher than 250 U per liter. Patients were excluded if they were receiving supplemental oxygen at a rate that exceeded 10 liters per minute, if they had a recent history of treatment with biologic agents or small-molecule immunosuppressive therapy, if they were receiving other immunosuppressive therapy that the investigator believed placed them at higher risk for an infection, or if they had had diverticulitis. The full list of entry criteria is provided in the protocol.

### RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 2:1 ratio to receive standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight administered intravenously, not to exceed 800 mg) or placebo; randomization was performed with randomly permuted blocks of sizes 3 and 6. Randomization was stratified according to site. Administration of tocilizumab or placebo was generally complete within 3 hours after informed consent was obtained.

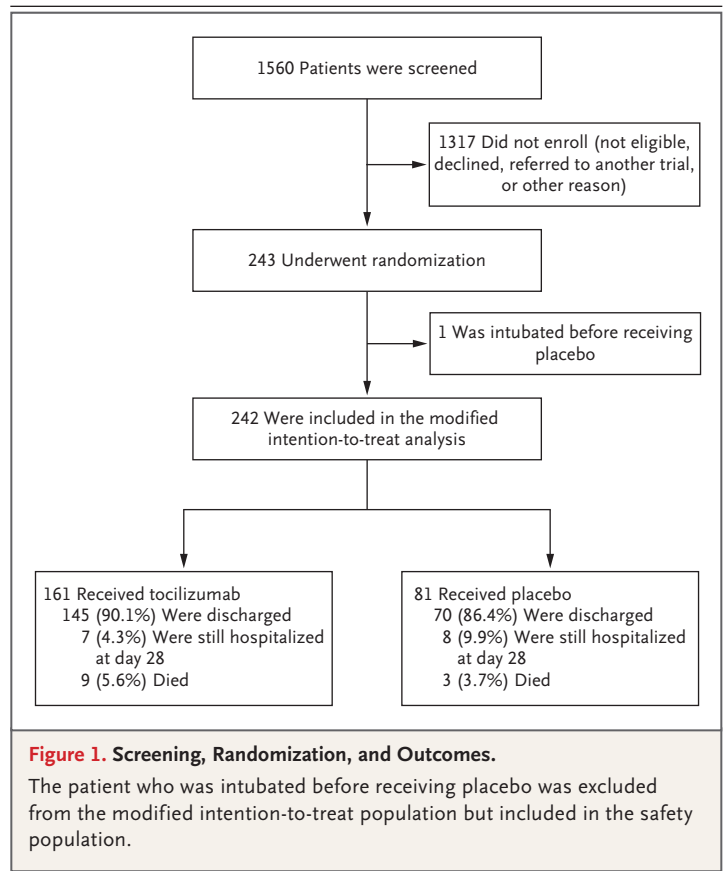
### CONCOMITANT TREATMENT

The results of the Adaptive Covid-19 Treatment Trial (ACTT-1) of remdesivir<sup>34</sup> became known during this trial, but the results of the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial<sup>35</sup> regarding the efficacy of dexamethasone were announced afterward. Therefore, some patients received remdesivir as concomitant treatment, whereas no patients received dexamethasone. Antiviral therapy, hydroxychloroquine, and glucocorticoids were permitted as concomitant treatment.

### OUTCOMES

The primary outcome was intubation (or death, for patients who died before intubation) after administration of tocilizumab or placebo, assessed in a time-to-event analysis. The first secondary outcome was clinical worsening, defined on the basis of an ordinal clinical improvement scale. Scores on the scale were defined as follows: 1, discharged or ready for discharge; 2, in (or ready for) a non-ICU hospital ward and not receiving supplemental oxygen; 3, in (or ready for) a non-ICU hospital ward and receiving supplemental oxygen; 4, in the ICU or a non-ICU hospital ward and receiving noninvasive ventilation or high-flow oxygen; 5, in the ICU, intubated, and receiving mechanical ventilation; 6, in the ICU and receiving extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; and 7, death (Table S2 in the Supplementary Appendix, available at NEJM.org). Worsening was defined as an increase by at least 1 point among patients who had been receiving supplemental oxygen at baseline or at least 2 points among those who had not been receiving supplemental oxygen at baseline. The second secondary outcome was discontinuation of supplemental oxygen among patients who had been receiving it at baseline. Both secondary outcomes were assessed in time-to-event analyses. Data from patients who were event-free at the end of follow-up were censored at 28 days (for the primary and first secondary outcome) or at 29 days (for the second secondary outcome). Data from patients who could not be reached for 28-day follow-up were censored at hospital discharge.

Tertiary outcomes were those related to other time-to-event analyses (e.g., improvement, discharge, or death), analyses of duration (supplemental oxygen use, receipt of mechanical venti-



lation), and binary outcomes (admission to the intensive care unit [ICU] or death). Exploratory analyses addressed the relationships among inflammatory biomarker levels, demographic and clinical features, and efficacy outcomes.

### STATISTICAL ANALYSIS

We assumed that the risk of invasive mechanical ventilation or death within 28 days would be 30% in the placebo group<sup>12</sup> and that the risk with tocilizumab would be reduced to 15%. With a total of 243 patients, we had 80% power to detect such a difference with the use of a log-rank test, assuming two-sided tests and a significance level of 0.05. A blinded interim analysis for safety was performed.

The statistical analysis and data-management plans are included with the protocol at NEJM.org. The primary efficacy analysis focused on the modified intention-to-treat population, defined as all patients who underwent randomization and received either tocilizumab or placebo before intubation or death. The safety population includ-

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Tocilizumab (N=161)	Placebo (N=82)	All Patients (N=243)
Enrolling hospital — no. (%)			
Boston Medical Center	16 (10)	7 (9)	23 (9)
Brigham and Women's Hospital	17 (11)	8 (10)	25 (10)
Lahey Hospital	2 (1)	2 (2)	4 (2)
Massachusetts General Hospital	62 (39)	30 (37)	92 (38)
North Shore Medical Center	51 (32)	26 (32)	77 (32)
Newton–Wellesley Hospital	13 (8)	7 (9)	20 (8)
St. Elizabeth's Medical Center	0	2 (2)	2 (1)
Median age (IQR) — yr	61.6 (46.4–69.7)	56.5 (44.7–67.8)	59.8 (45.3–69.4)
Age >65 yr — no. (%)	60 (37)	22 (27)	82 (34)
Male sex — no. (%)	96 (60)	45 (55)	141 (58)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	1 (1)	0	1 (<1)
Asian	7 (4)	2 (2)	9 (4)
Black	24 (15)	16 (20)	40 (16)
Native Hawaiian or Pacific Islander	0	1 (1)	1 (<1)
White	71 (44)	33 (40)	104 (43)
Other	35 (22)	15 (18)	50 (21)
Unknown	23 (14)	15 (18)	38 (16)
Hispanic or Latino ethnic group — no. (%)‡			
Hispanic or Latino	70 (43)	39 (48)	109 (45)
Not Hispanic or Latino	84 (52)	35 (43)	119 (49)
Unknown	7 (4)	8 (10)	15 (6)
Median BMI (IQR)‡	29.9 (26.0–34.2)	30.2 (25.7–33.8)	30.1 (25.9–34.2)
BMI ≥30 — no. (%)‡	80 (50)	42 (51)	122 (50)
Median time from symptom onset to randomization (IQR) — days	9.0 (6.0–13.0)	10.0 (7.0–13.0)	9.0 (6.0–13.0)
Hypertension — no. (%)	80 (50)	38 (46)	118 (49)
Heart failure — no. (%)	17 (11)	7 (9)	24 (10)
History of myocardial infarction — no. (%)	15 (9)	6 (7)	21 (9)
Chronic obstructive pulmonary disorder — no. (%)	15 (9)	7 (9)	22 (9)
Asthma — no. (%)	15 (9)	7 (9)	22 (9)
Smoking status — no. (%)			
Current smoker	7 (4)	0	7 (3)
Former smoker	46 (29)	26 (32)	72 (30)
Lifelong nonsmoker	99 (61)	48 (59)	147 (60)
Unknown	9 (6)	8 (10)	17 (7)
Diabetes — no. (%)	45 (28)	30 (37)	75 (31)
Chronic kidney disease — no. (%)	29 (18)	13 (16)	42 (17)
History of cancer — no. (%)	22 (14)	8 (10)	30 (12)

**Table 1. (Continued)**

Characteristic	Tocilizumab (N=161)	Placebo (N=82)	All Patients (N=243)
Ordinal scale score — no. (%)§			
2	23 (14)	15 (18)	38 (16)
3	133 (83)	61 (74)	194 (80)
4	5 (3)	5 (6)	10 (4)
5	0	1 (1)	1 (<1)
Median laboratory values (IQR)¶			
Absolute lymphocyte count — cells/mm <sup>3</sup>	1040 (700–1400)	1030 (680–1360)	1030 (700–1400)
C-reactive protein level — mg/liter	116.0 (67.1–190.6)	94.3 (58.4–142.0)	110.0 (64.9–175.3)
Ferritin level — ng/ml	723 (413–1212)	686 (382–1228)	708 (411–1225)
D-Dimer level — ng/ml	857 (536–1695)	980 (500–1739)	884 (527–1730)
Lactate dehydrogenase level — U/liter	351 (287–420)	324 (290–395)	340 (289–413)
Serum interleukin-6 level — pg/ml	23.6 (14.0–49.9)	25.4 (14.6–40.3)	24.4 (14.1–45.5)
Erythrocyte sedimentation rate — mm/hr	61 (42–90)	63 (42–87)	61 (42–88)
Troponin level — ng/liter	8 (6–22)	9 (6–24)	9 (6–22)
NT-proBNP level — pg/ml	110 (50–438)	93 (33–431)	108 (38–437)
Procalcitonin level — ng/ml	0.2 (0.1–0.4)	0.2 (0.1–0.3)	0.2 (0.1–0.4)

\* Percentages may not total 100 because of rounding. IQR denotes interquartile range, and NT-proBNP N-terminal pro-B-type natriuretic peptide.

† Race and ethnic group were reported by the patients.

‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ Scores on the ordinal clinical improvement scale range from 1 to 7, with higher scores indicating worse clinical condition. A score of 2 indicates that the patient was in (or ready for) a non-intensive care unit (ICU) hospital ward and was not receiving supplemental oxygen; a score of 3, that the patient was in (or ready for) a non-ICU hospital ward and was receiving supplemental oxygen; a score of 4, that the patient was in the ICU or in a non-ICU hospital ward and was receiving noninvasive ventilation or high-flow oxygen; and a score of 5, that the patient was in the ICU, intubated, and receiving mechanical ventilation.

¶ Absolute lymphocyte counts were missing for 2 patients (1 in the tocilizumab group and 1 in the placebo group), C-reactive protein levels were missing for 2 patients (1 and 1), ferritin levels were missing for 1 patient (in the placebo group), D-dimer levels were missing for 2 patients (1 and 1), lactate dehydrogenase levels were missing for 3 patients (1 and 2), interleukin-6 levels were missing for 9 patients (6 and 3), erythrocyte sedimentation rates were missing for 24 patients (19 and 5), troponin levels were missing for 9 patients (5 and 4), NT-proBNP levels were missing for 19 patients (12 and 7), and procalcitonin levels were missing for 16 patients (8 and 8).

ed all patients who underwent randomization and received either tocilizumab or placebo. For primary and secondary outcomes, the treatment groups were compared with the use of log-rank tests stratified according to site. The three smallest sites were combined. The differences between the treatment groups were estimated as hazard ratios with 95% confidence intervals from stratified Cox proportional hazards models. Estimates of the percentages of patients who had events at specific time points were based on the corresponding Kaplan–Meier curves. The proportional hazards assumption was confirmed through correlation tests between the weighted Schoenfeld residuals and event times.

A single primary analysis was performed with the criterion for statistical significance defined as a two-sided P value of less than 0.05. Testing of the two secondary efficacy outcomes was performed with a Bonferroni–Holm correction to ensure an overall two-sided significance level of less than 0.05. No corrections for multiplicity were used for tertiary and exploratory analyses. Confidence intervals were not adjusted for multiple comparisons and cannot be used to infer effects. We examined whether the treatment effect on the primary outcome varied within subgroups defined on the basis of demographic or clinical risk factors for poor Covid-19 outcomes. Treatment-effect modification was assessed in

**Table 2. Time-to-Event Outcomes in the Modified Intention-to-Treat Population.\***

Outcome	No. of Patients with Event within 28 Days	Percentage of Patients with Event (95% CI) <sup>†</sup>		Median No. of Days to Event (95% CI)	Hazard Ratio (95% CI)	Log-Rank P Value <sup>‡</sup>
Measures of worsening						
Primary outcome: mechanical ventilation or death						
Tocilizumab	17	9.9 (6.2–15.7)	10.6 (6.7–16.6)	NR	0.83 (0.38–1.81)	0.64
Placebo	10	10.0 (5.1–18.9)	12.5 (6.9–22.0)	NR		
Secondary outcome: clinical worsening on ordinal scale <sup>§</sup>						
Tocilizumab	31	18.0 (12.9–24.9)	19.3 (14.0–26.2)	NR	1.11 (0.59–2.10)	0.73
Placebo	14	14.9 (8.7–24.7)	17.4 (10.7–27.7)	NR		
Tertiary outcome: mechanical ventilation <sup>¶</sup>						
Tocilizumab	11	6.8 (3.6–11.4)	6.8 (3.6–11.4)	NR	0.65 (0.26–1.62)	—
Placebo	8	10.0 (4.6–17.7)	10.0 (4.6–17.7)	NR		
Tertiary outcome: death						
Tocilizumab	9	4.4 (2.1–8.9)	5.6 (3.0–10.5)	NR	1.52 (0.41–5.61)	—
Placebo	3	1.3 (0.2–8.7)	3.8 (1.2–11.3)	NR		
Measures of improvement						
Secondary outcome: discontinuation of supplemental oxygen among patients receiving it at baseline						
Tocilizumab	114	75.4 (67.9–82.2)	82.6 (75.9–88.4)	5.0 (3.8–7.6)	0.94 (0.67–1.30)	0.69
Placebo	56	78.8 (68.3–87.7)	84.9 (75.2–92.2)	4.9 (3.8–7.8)		
Tertiary outcome: clinical improvement on ordinal scale <sup>§</sup>						
Tocilizumab	147	86.3 (80.6–91.1)	91.3 (86.3–95.1)	6.0 (5.0–6.0)	1.06 (0.80–1.41)	—
Placebo	72	81.5 (72.4–89.0)	88.9 (81.0–94.5)	5.0 (4.0–7.0)		
Tertiary outcome: initial discharge						
Tocilizumab	147	86.3 (80.6–91.1)	91.3 (86.3–95.0)	6.0 (4.0–7.0)	1.08 (0.81–1.43)	—
Placebo	72	81.5 (72.4–89.0)	88.9 (81.0–94.5)	6.0 (5.0–6.0)		

\* The modified intention-to-treat population included the 242 patients (161 in the tocilizumab group and 81 in the placebo group) who underwent randomization and received either tocilizumab or placebo before intubation or death. NR denotes not reached.

† Percentages were estimated from the Kaplan–Meier curve.

‡ P values are not reported for tertiary outcomes.

§ Worsening was defined as an increase in score on the ordinal clinical improvement scale by at least 1 point among patients receiving supplemental oxygen at baseline or at least 2 points among those not receiving supplemental oxygen at baseline. Improvement was defined as an increase in score by at least 2 points.

¶ Results for the time-to-event analysis of mechanical ventilation were obtained with the use of competing-risks analyses with death treated as a competing event. The percentage of patients with an event was estimated from the cumulative incidence function for the event of interest (mechanical ventilation). The cause-specific hazard ratio is reported.



**Figure 2. Kaplan–Meier Analyses of Efficacy Outcomes.**

Shown are Kaplan–Meier curves for the time-to-event analyses of mechanical ventilation or death (Panel A); clinical worsening, defined as an increase in score on an ordinal clinical improvement scale (scores range from 1 to 7, with higher scores indicating worse clinical condition) by at least 1 point among patients who had been receiving supplemental oxygen at baseline or at least 2 points among those who had not been receiving supplemental oxygen at baseline (Table S2) (Panel B); and discontinuation of supplemental oxygen among patients who had been receiving it at baseline (Panel C).

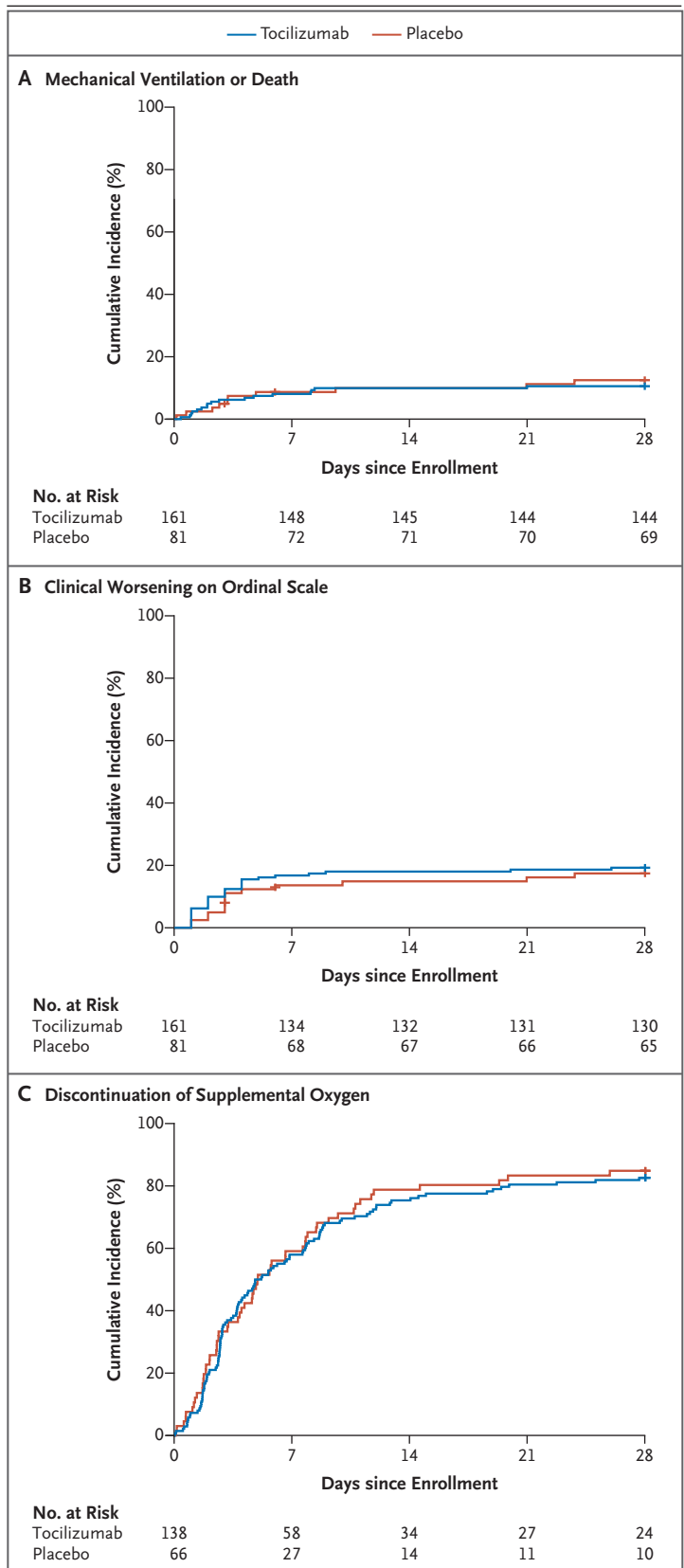
separate interaction models for each risk factor. Each model was stratified according to site and included age ( $>65$  or  $\leq 65$  years), sex, Hispanic or Latino ethnic group, and race (White or non-White) as covariates. We also evaluated the association between these risk factors and the primary outcome in separate main effects models with stratification and covariate adjustment.

## RESULTS

**PATIENTS**

Between April 20 and June 15, 2020, a total of 243 patients were enrolled; 161 received tocilizumab, and 81 received placebo (Fig. 1). One patient, who had been intubated before receiving placebo, was excluded from the modified intention-to-treat population but was included in the safety population. The baseline characteristics of the patients are shown in Table 1. In the modified intention-to-treat population, 141 patients (58%) were male and 102 patients (42%) were female. The median age was 59.8 years (interquartile range, 45.3 to 69.4). The youngest patient was 21.7 years of age, and the oldest was 85.4 years of age. In the overall trial population, 45% of patients were Hispanic or Latino, 16% were Black, and 43% were White.

The body-mass index (the weight in kilograms divided by the square of the height in meters) was at least 30 in 51% of the patients at baseline, 49% of the patients had hypertension, and 31% had known diabetes mellitus. A total of 194 patients (80%) were hospitalized in non-ICU hospital wards and were receiving supplemental oxygen ( $\leq 6$  liters per minute), delivered by nasal cannula, to maintain an oxygen saturation greater than 92%; 10 (4%) were receiving high-flow oxygen ( $>6$  and  $\leq 10$  liters per minute delivered by any



**Table 3. Duration Outcomes and Admission to the ICU or Death in the Modified Intention-to-Treat Population.**

Outcome	Tocilizumab (N=161)	Placebo (N=81)	Relative Risk
Median duration of receipt of supplemental oxygen (IQR) — days*	4.0 (1.8–11.6)	3.9 (1.1–9.2)	—
Median duration of mechanical ventilation (IQR) — days†	15.0 (12.6–NR)	27.9 (16.3–NR)	—
Admission to ICU or death — %	15.9	15.8	0.97 (0.50–1.88)

\* Patients who did not receive supplemental oxygen were assigned a value of 0. Patients who died before discontinuation of supplemental oxygen were assigned a value equal to the number of days from when supplemental oxygen began until the end of the 28-day follow-up period.

† The median and IQR for duration of mechanical ventilation were estimated from Kaplan–Meier curves generated within patients who received mechanical ventilation (11 in the tocilizumab group and 8 in the placebo group). Data for patients who died without discontinuation of mechanical ventilation were censored at 28 days.

device); and 38 (16%) were not receiving supplemental oxygen at baseline. The median concentration of C-reactive protein was 110.0 mg per liter (interquartile range, 64.9 to 175.3); ferritin, 708 ng per milliliter (interquartile range, 411 to 1225); D-dimer, 884 ng per milliliter (interquartile range, 527 to 1730); and lactate dehydrogenase, 340 U per liter (interquartile range, 289 to 413).

Similar percentages of patients in the two groups received remdesivir, hydroxychloroquine, or glucocorticoids. Remdesivir was administered to 77 patients (53 [33%] in the tocilizumab group and 24 [29%] in the placebo group). Hydroxychloroquine was administered to 9 patients (6 [4%] in the tocilizumab group and 3 [4%] in the placebo group). Glucocorticoids were administered to 23 patients (18 [11%] in the tocilizumab group and 5 [6%] in the placebo group).

#### PRIMARY OUTCOME

A total of 27 patients (11.2%) were intubated within 28 days or died before intubation (Table 2). At day 28, 17 patients (10.6%) in the tocilizumab group and 10 patients (12.5%) in the placebo group had been intubated or had died (11 were intubated and 6 died without being intubated in the tocilizumab group; 8 were intubated and 2 died without being intubated in the placebo group). The Kaplan–Meier curves for the time to intubation or death are shown in Figure 2A. The hazard ratio for a primary outcome event in the tocilizumab group was 0.83 (95% confidence interval [CI], 0.38 to 1.81;  $P=0.64$  by log-rank test). The hazard ratio was also estimated with adjustment for age, sex, race, Hispanic or

Latino ethnic group, diabetes status, and baseline serum interleukin-6 concentration. The adjusted hazard ratio was 0.66 (95% CI, 0.28 to 1.52). The difference between the adjusted and unadjusted hazard ratios was primarily due to the greater percentage of older patients in the tocilizumab group.

#### SECONDARY OUTCOMES

The Kaplan–Meier curves for the time to worsening on the ordinal clinical improvement scale are shown in Figure 2B. The hazard ratio for worsening in the tocilizumab group as compared with the placebo group was 1.11 (95% CI, 0.59 to 2.10;  $P=0.73$  by log-rank test) (Table 2). The adjusted hazard ratio was 0.88 (95% CI, 0.45 to 1.72). At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had had disease worsening as measured on the ordinal scale. At 28 days, the percentages were 19.3% and 17.4%, respectively.

The Kaplan–Meier curves for the time to discontinuation of supplemental oxygen among patients who had been receiving it at baseline are shown in Figure 2C. The hazard ratio for discontinuation by 28 days in the tocilizumab group as compared with the placebo group was 0.94 (95% CI, 0.67 to 1.30;  $P=0.69$  by log-rank test). The adjusted hazard ratio was 0.95 (95% CI, 0.67 to 1.33). The median time to discontinuation of supplemental oxygen among patients who had been receiving it at baseline was 5.0 days (interquartile range, 3.8 to 7.6) in the tocilizumab group and 4.9 days (interquartile range, 3.8 to 7.8) in the placebo group. At 14 days, 75.4% of pa-



tients in the tocilizumab group and 78.8% in the placebo group were no longer receiving supplemental oxygen. At 28 days, the percentages were 82.6% and 84.9%, respectively.

### TERTIARY AND EXPLORATORY OUTCOMES

Tertiary efficacy outcomes are shown in Tables 2 and 3. None of the outcomes differed substantially between the treatment groups. The median time to improvement was 6.0 days (95% CI, 5.0 to 6.0) in the tocilizumab group and 5.0 days (95% CI, 4.0 to 7.0) in the placebo group. The median duration of supplemental oxygen use after administration of tocilizumab was 4.0 days; the corresponding measure in the placebo group was 3.9 days. Among the 233 patients who were not in the ICU at enrollment, 25 patients (15.9%) in the tocilizumab group and 12 patients (15.8%) in the placebo group were either admitted to the ICU or died before ICU admission. Among the 19 patients who were intubated, the duration of mechanical ventilation did not differ significantly between the groups (median duration, 15.0 days in the tocilizumab group and 27.9 days in the placebo group). The median time to discharge was 6.0 days in both groups. The results of exploratory analyses of changes in the concentrations of inflammatory markers over time are shown in Table S3.

### PATIENT AND TREATMENT SUBGROUP ANALYSES

Multivariate, adjusted models showed that patients older than 65 years of age were at greater risk for progression to intubation or death than younger patients (hazard ratio, 3.11; 95% CI, 1.36 to 7.10). In addition, patients with baseline serum interleukin-6 concentrations higher than 40 pg per milliliter were more likely to have progression than those with baseline concentrations at or below 40 pg per milliliter (hazard ratio, 3.03; 95% CI, 1.34 to 6.83). Factors that were not found to affect the risk of intubation or death included male sex (hazard ratio, 1.27; 95% CI, 0.57 to 2.81), Hispanic or Latino ethnic group (hazard ratio, 1.16; 95% CI, 0.47 to 2.85), obesity (hazard ratio, 1.32; 95% CI, 0.60 to 2.90), diabetes (hazard ratio, 1.55; 95% CI, 0.69 to 3.48), and treatment with remdesivir (hazard ratio, 1.95; 95% CI, 0.86 to 4.44). No difference between the subgroups was observed for the treatment effect (Table S4).

**Table 4. Adverse Events in the Safety Population.\***

Event	Tocilizumab (N=161)	Placebo (N=82)	P Value
<i>no. of patients (%)</i>			
Death	9 (5.6)	4 (4.9)†	0.81
Hypersensitivity reaction to infusion	2 (1.2)	2 (2.4)	0.52
Infection of grade ≥3	13 (8.1)	14 (17.1)	0.03
Grade 3	12 (7.5)	14 (17.1)	
Grade 4	1 (0.6)	0	
Myocardial infarction	0	1 (1.2)	0.15
Deep venous thrombosis	2 (1.2)	3 (3.7)	0.18
Pulmonary embolism	2 (1.2)	2 (2.4)	0.47
Stroke	2 (1.2)	0	0.31
Seizure	0	1 (1.2)	0.13
Arterial ischemia	1 (0.6)	0	0.49
Gastrointestinal perforation	0	0	—
Demyelinating disorder	0	0	—
Elevated liver-function values			
ALT, grade ≥3	8 (5.0)	4 (4.9)	0.99
Grade 3	8 (5.0)	4 (4.9)	
Grade 4	0	0	
AST, grade ≥3	6 (3.7)	3 (3.7)	0.99
Grade 3	6 (3.7)	2 (2.4)	
Grade 4	0	1 (1.2)	
Neutropenia, grade ≥3	22 (13.7)	1 (1.2)	0.002
Grade 3	21 (13.0)	1 (1.2)	
Grade 4	1 (0.6)	0	
Thrombocytopenia, grade ≥3	1 (0.6)	0	0.51
Grade 3	1 (0.6)	0	
Grade 4	0	0	
Bleeding	0	1 (1.2)	0.15
Other‡	21 (13.0)	14 (17.1)	0.15

\* The percentage of patients who had at least one occurrence of each type of adverse event is reported. Grade was calculated as the maximum grade reported across occurrences within a patient. The percentages of patients with adverse events were compared with the use of a Mantel-Haenszel test stratified according to enrolling site without adjustment for multiple comparisons. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

† One patient who died was intubated before receiving placebo and was excluded from the modified intention-to-treat population but included in the safety population.

‡ Other events are listed in detail in Table S6.

### SAFETY

Adverse events are shown in Table 4. No new safety signal for tocilizumab emerged. Neutrope-

nia developed in 22 patients in the tocilizumab group, as compared with only 1 patient in the placebo group ( $P=0.002$ ), but serious infections occurred in fewer patients in the tocilizumab group (13 [8.1%] vs. 14 [17.3%];  $P=0.03$ ). There were 36 serious adverse events in the tocilizumab group, occurring in a total of 28 patients. Of these 36 serious adverse events, 25 were considered by the investigators to be unrelated to tocilizumab, and 11 were considered to be related or possibly related. There were 38 serious adverse events in the placebo group, occurring in 12 patients; 35 events were considered unrelated to placebo, and 3 were considered related or possibly related. All serious adverse events are listed in Table 4. They are also listed separately with additional descriptions in Table S5.

## DISCUSSION

Our data do not provide support for the concept that early interleukin-6 receptor blockade is an effective treatment strategy in moderately ill patients hospitalized with Covid-19. The hypothesis underlying our trial was that interleukin-6 receptor blockade in patients with disease that had not yet led to intubation would disrupt the cytokine storm associated with Covid-19, thereby preventing the most severe disease consequences. Findings from this randomized, double-blind, placebo-controlled trial indicated that this intervention had no significant effect on the risk of intubation or death, on disease worsening, on time to discontinuation of supplemental oxygen, or on any of the efficacy outcomes we examined. Because of the width of the confidence intervals for our efficacy comparisons, however, we cannot exclude the possibility that tocilizumab treatment is associated with either some benefit or harm in some patients.

Our results stand in contrast to those of multiple open-label trials and nonrandomized case series, some of which have suggested that interleukin-6 receptor blockade has a substantial positive effect on patients with Covid-19. Reported but still unpublished results of a small number of other randomized trials have been discouraging.<sup>36,37</sup> The explanation for the failure of tocilizumab to affect clinical outcomes substantially in our trial is not clear. One possibility is that interleukin-6 and other inflammatory proteins that are observed to be present at elevated

levels in patients with Covid-19 represent host responses to the infection, similar to the elevations in cytokine levels seen in patients with endocarditis, sepsis, and other infections, rather than components of a self-amplifying inflammatory loop that would benefit from suppression. Regardless of the explanation, our findings in the context of information about other randomized, blinded trials of interleukin-6 receptor blockade largely undermine the concept that this anti-cytokine approach is a useful treatment strategy for preventing the evolution of Covid-19 from a moderate to a severe state. It remains possible, however, that patient populations that differ from the one targeted by our trial might benefit from interleukin-6 receptor blockade. It is also possible that other anticytokine approaches or studies in which alternative antiinflammatory or antiviral strategies (or combinations of those strategies) are used will show greater efficacy than we have shown. The overall experience with interleukin-6 receptor blockade, however, underscores the point that any such approach must be subjected to randomized, blinded trials. Moreover, such investigations should be performed early in the course of evaluating each strategy, before the adoption of widespread use.<sup>38</sup>

Our results confirmed the relationship between older age and poor outcomes in Covid-19 but did not identify separate effects of sex, diabetes, obesity, or Hispanic or Latino ethnic group on prognosis. We also confirmed that patients with higher serum interleukin-6 concentrations at baseline were more likely to have a poor outcome.<sup>10,11</sup> Although tocilizumab did not show efficacy in this trial, the drug was not associated with excessive high-grade toxic effects in this population, which was characterized by multiple coexisting conditions. Patients treated with tocilizumab had fewer serious infections than those who received placebo.

Our trial has a number of strengths. It was a randomized, double-blind, placebo-controlled trial focusing on hospitalized patients who had not been intubated. The trial population was also ethnically diverse, including substantial numbers of Hispanic or Latino patients.<sup>39,40</sup>

The trial also has certain weaknesses. The primary event rate we observed was lower than anticipated, perhaps because of evolving standards of care during the trial. Remdesivir became available early in the trial, and general

approaches to management were also approved, including strategies to delay intubation, if possible, rather than intubating early. Nevertheless, 12% of the patients in our trial were intubated or died, and we found little evidence that tocilizumab altered any efficacy outcomes. Despite randomization, imbalance in the percentage of older patients between the treatment groups was observed. This had some effect on the estimated treatment effect on the primary outcome, as evidenced by the difference between the unadjusted and adjusted hazard ratios. However, the confidence intervals in both analyses were wide,

and the overall conclusions of the unadjusted and adjusted analyses are consistent.

In this randomized, double-blind, placebo-controlled trial, we did not find any efficacy of interleukin-6 receptor blockade for the treatment of hospitalized patients with Covid-19.

Supported by Genentech.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who participated in the trial, Payal S. Patel, John B. Montana, and the nurses and staff of the Translational Clinical Research Center at the Massachusetts General Hospital.

## APPENDIX

The authors' full names and academic degrees are as follows: John H. Stone, M.D., M.P.H., Matthew J. Frigault, M.D., Naomi J. Serling-Boyd, M.D., Ana D. Fernandes, M.A., Liam Harvey, B.S., Andrea S. Foulkes, Ph.D., Nora K. Horick, M.S., Brian C. Healy, Ph.D., Ruta Shah, M.D., Ana Maria Bensaci, M.D., Ann E. Woolley, M.D., Sarah Nikiforow, M.D., Ph.D., Nina Lin, M.D., Manish Sagar, M.D., Harry Schrager, M.D., David S. Huckins, M.D., Matthew Axelrod, M.D., Michael D. Pincus, D.O., Jorge Fleisher, M.D., Chana A. Sacks, M.D., M.P.H., Michael Dougan, M.D., Ph.D., Crystal M. North, M.D., M.P.H., Yuan-Di Halvorsen, Ph.D., Tara K. Thurber, B.S., Zeina Dagher, Ph.D., Allison Scherer, Ph.D., Rachel S. Wallwork, M.D., Arthur Y. Kim, M.D., Sara Schoenfeld, M.D., Pritha Sen, M.D., Thomas G. Neilan, M.D., M.P.H., Cory A. Perugino, D.O., Sebastian H. Unizony, M.D., Deborah S. Collier, M.D., Mark A. Matza, M.D., Janeth M. Vinh, M.D., Kathryn A. Bowman, M.D., Eric Meyerowitz, M.D., Amna Zafar, M.D., Zsafia D. Drobni, M.D., Marcy B. Bolster, M.D., Minna Kohler, M.D., Kristin M. D'Silva, M.D., Jonathan Dau, M.D., Megan M. Lockwood, M.D., Caroline Cubbison, M.D., Brittany N. Weber, M.D., Ph.D., and Michael K. Mansour, M.D., Ph.D.

The authors' affiliations are as follows: Massachusetts General Hospital (J.H.S., M.J.F., N.J.S.-B., A.D.F., L.H., A.S.F., N.K.H., B.C.H., C.A.S., M.D., C.M.N., Y.-D.H., T.K.T., Z.D., A.S., R.S.W., A.Y.K., S.S., P.S., T.G.N., C.A.P., S.H.U., D.S.C., M.A.M., J.M.Y., K.A.B., E.M., A.Z., Z.D.D., M.B.B., M.K., K.M.D., J.D., M.M.L., M.K.M.), Brigham and Women's Hospital (A.E.W., S.N., B.N.W.), and Boston Medical Center (N.L., M.S.), Boston, North Shore Medical Center, Salem (R.S., A.M.B., C.C.), Newton-Wellesley Hospital, Newton (H.S., D.S.H.), Beth Israel Lahey Health, Burlington (M.A., M.D.P.), and St. Elizabeth's Medical Center, Brighton (J.F.) — all in Massachusetts.

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