

Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia

A Randomized Clinical Trial

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IMPORTANCE The coronavirus disease 2019 (COVID-19) pandemic is threatening billions of people worldwide. Tocilizumab has shown promising results in retrospective studies in patients with COVID-19 pneumonia with a good safety profile.

OBJECTIVE To evaluate the effect of early tocilizumab administration vs standard therapy in preventing clinical worsening in patients hospitalized with COVID-19 pneumonia.

DESIGN, SETTING, AND PARTICIPANTS Prospective, open-label, randomized clinical trial that randomized patients hospitalized between March 31 and June 11, 2020, with COVID-19 pneumonia to receive tocilizumab or standard of care in 24 hospitals in Italy. Cases of COVID-19 were confirmed by polymerase chain reaction method with nasopharyngeal swab. Eligibility criteria included COVID-19 pneumonia documented by radiologic imaging, partial pressure of arterial oxygen to fraction of inspired oxygen (P_{aO_2}/F_{iO_2}) ratio between 200 and 300 mm Hg, and an inflammatory phenotype defined by fever and elevated C-reactive protein.

INTERVENTIONS Patients in the experimental arm received intravenous tocilizumab within 8 hours from randomization (8 mg/kg up to a maximum of 800 mg), followed by a second dose after 12 hours. Patients in the control arm received supportive care following the protocols of each clinical center until clinical worsening and then could receive tocilizumab as a rescue therapy.

MAIN OUTCOME AND MEASURES The primary composite outcome was defined as entry into the intensive care unit with invasive mechanical ventilation, death from all causes, or clinical aggravation documented by the finding of a P_{aO_2}/F_{iO_2} ratio less than 150 mm Hg, whichever came first.

RESULTS A total of 126 patients were randomized (60 to the tocilizumab group; 66 to the control group). The median (interquartile range) age was 60.0 (53.0-72.0) years, and the majority of patients were male (77 of 126, 61.1%). Three patients withdrew from the study, leaving 123 patients available for the intention-to-treat analyses. Seventeen patients of 60 (28.3%) in the tocilizumab arm and 17 of 63 (27.0%) in the standard care group showed clinical worsening within 14 days since randomization (rate ratio, 1.05; 95% CI, 0.59-1.86). Two patients in the experimental group and 1 in the control group died before 30 days from randomization, and 6 and 5 patients were intubated in the 2 groups, respectively. The trial was prematurely interrupted after an interim analysis for futility.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial of hospitalized adult patients with COVID-19 pneumonia and P_{aO_2}/F_{iO_2} ratio between 200 and 300 mm Hg who received tocilizumab, no benefit on disease progression was observed compared with standard care. Further blinded, placebo-controlled randomized clinical trials are needed to confirm the results and to evaluate possible applications of tocilizumab in different stages of the disease.

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Presentations of coronavirus disease 2019 (COVID-19) range from asymptomatic to severe pneumonia with respiratory failure that can lead to invasive mechanical ventilation and/or death.^{1,2} In patients with COVID-19 and severe lung disease, hyperinflammation is frequently observed, with an increased plasma concentrations of various pro-inflammatory cytokines, including interleukin (IL)-6, and acute phase reactants.³⁻⁵ This exaggerated inflammatory response caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents one of the most important negative prognostic factors in these patients.⁶

During the first months of the pandemic, the treatment of COVID-19 was based on symptoms, with supportive care in intensive care units (ICUs) for patients with more severe disease. Recently, the RECOVERY randomized clinical trial⁷ showed that a pharmacologic anti-inflammatory treatment, dexamethasone, reduces the risk of death in patients with COVID-19 pneumonia who are receiving respiratory support. This reinforces the idea that therapies targeting cytokines involved in the excessive inflammatory response related to SARS-CoV-2 infection may have an important role in blunting hyperinflammation and containing lung damage. Given the association of elevated IL-6 levels with severe COVID-19 and mortality, therapy with biologic agents blocking IL-6 seems to be a promising treatment for COVID-19.^{5,6,8}

Tocilizumab is a recombinant humanized monoclonal antibody directed against both the soluble and the membrane-bound IL-6 receptor. It is indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, and life-threatening cytokine release syndrome induced by chimeric antigen receptor T-cells.⁹⁻¹² Recent retrospective studies have suggested that tocilizumab may be associated with lower risk of death or intubation in patients with severe COVID-19 pneumonia.¹³⁻¹⁷ However, the observational nature of these studies hampers the assessment of the effect of tocilizumab. To evaluate the efficacy and safety of early administration of tocilizumab in hospitalized patients with COVID-19 pneumonia, we designed and conducted a multicentric randomized clinical trial (eMethods in Supplement 1).

Methods

Design

This is a multicenter, open-label randomized clinical trial aimed at assessing the efficacy of early administration of tocilizumab vs standard therapy in hospitalized patients with COVID-19 pneumonia. The trial protocol and statistical analysis plan appear in Supplement 2 and Supplement 3. A total of 24 Italian centers enrolled patients between March 31 and June 11, 2020. Patients were randomized using a web-based system with a 1:1 allocation ratio. Randomization was stratified by center (Figure 1). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Patients

We enrolled hospitalized patients 18 years and older, with an instrumental diagnosis of COVID-19 pneumonia confirmed by a

Key Points

Question Does early tocilizumab administration prevent clinical worsening in patients hospitalized with coronavirus disease 2019 (COVID-19) pneumonia?

Findings In this randomized clinical trial of 126 patients with a partial pressure of arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FIO}_2$) ratio between 200 and 300 mm Hg at enrollment, the rate of the primary clinical end point (clinical worsening) was not significantly different between the control group and the tocilizumab group.

Meaning The administration of tocilizumab in patients with COVID-19 pneumonia and a $\text{PaO}_2/\text{FIO}_2$ ratio between 200 and 300 mm Hg did not reduce the risk of clinical worsening; further blinded, placebo-controlled randomized clinical trials are needed to confirm the results and to evaluate possible applications of tocilizumab in different stages of the disease.

positive reverse-transcriptase polymerase chain reaction assay for SARS-CoV-2 in a respiratory tract specimen. Other inclusion criteria were the presence of acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FIO}_2$) ratio between 200 and 300 mm/Hg, an inflammatory phenotype defined by a temperature greater than 38 °C during the last 2 days, and/or serum C-reactive protein (CRP) levels of 10 mg/dL or greater and/or CRP level increased to at least twice the admission measurement. Patients at enrollment were allowed to receive oxygen therapy with Venturi mask or high-flow nasal cannula with recorded and preset FIO_2 , but not invasive or non-invasive mechanical ventilation. All patients had arterial blood gas analysis to monitor $\text{PaO}_2/\text{FIO}_2$ ratio.

Exclusion criteria included ICU admission, known hypersensitivity to tocilizumab, and any condition preventing future admission to ICU, such as advanced age with multiple comorbidities, as well as the patient's expressed will to avoid future intubation. The detailed inclusion and exclusion criteria are reported in the trial protocol in Supplement 2. After randomization, patients were allowed to receive supplemental oxygen therapy, including noninvasive ventilation, according to clinical needs.

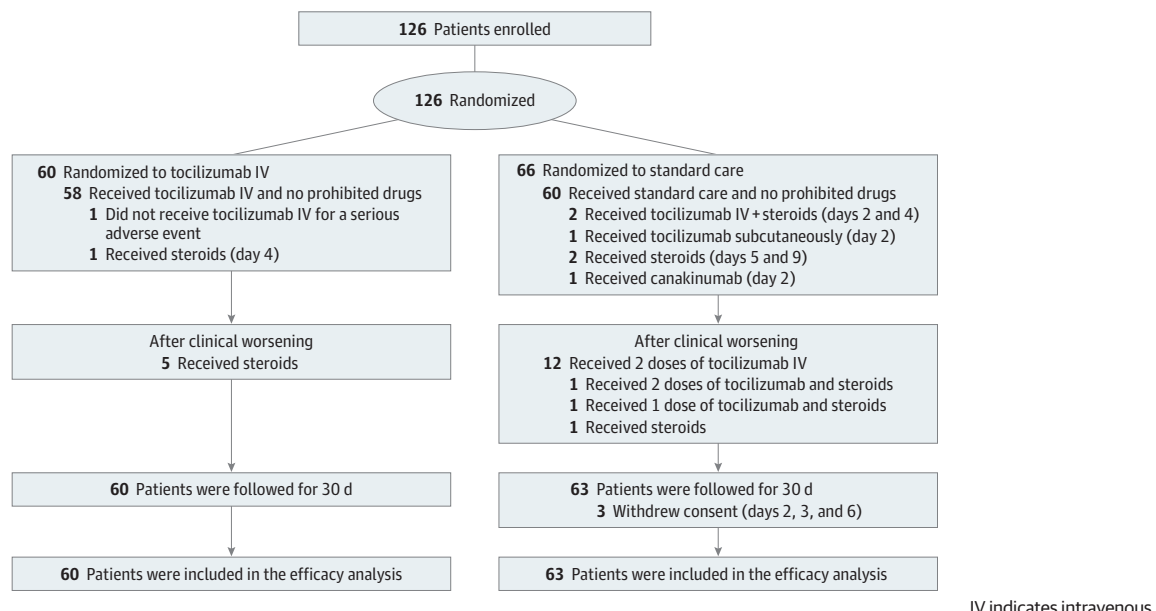
Objectives

The primary aim was to evaluate the efficacy of early administration of tocilizumab vs standard therapy in the first 2 weeks since randomization. The primary end point was clinical worsening within 14 days since randomization, defined by the occurrence of 1 of the following events, whichever occurred first:

- Admission to ICU with mechanical ventilation
- Death from any cause
- $\text{PaO}_2/\text{FIO}_2$ ratio less than 150 mm Hg in 1 of the scheduled arterial blood gas measurements or in an emergency measurement, confirmed within 4 hours by a second examination

Criteria for institution of mechanical ventilation were $\text{PaO}_2/\text{FIO}_2$ ratio less than 150 mm Hg, respiratory rate greater than 30 breaths/min, signs of respiratory distress, or multiorgan failure. Secondary aims included the evaluation of the efficacy of early vs late administration of tocilizumab in

Figure 1. Flowchart of the Study



admission to ICU with mechanical ventilation, mortality, and tocilizumab toxic effects.

Treatment

The experimental arm received tocilizumab intravenously within 8 hours from randomization at a dose of 8 mg/kg up to a maximum of 800 mg, followed by a second dose after 12 hours. Patients in the control arm received supportive care following the treatment protocols of each center. All drugs were allowed but IL-1 blockers, Jak inhibitors, and tumor necrosis factor inhibitors. Steroids were allowed if already taken before hospitalization. In case of occurrence of documented clinical worsening, patients randomized in both arms could receive any therapy, including steroids, and, for patients randomized in the control arm, tocilizumab.

Procedures

All patients were assessed from randomization (day 1) through day 14. Adverse events were recorded from time of signature of informed consent and graded according to the Common Terminology Criteria for Adverse Events, version 5.0. Causality was assessed by the investigators for serious adverse events.

Ethics

The trial was submitted and approved March 27, 2020, by the Italian Medicines Agency (AIFA) and by the COVID-19 Ethics Committee established at the National Institute for Infectious Diseases, Lazzaro Spallanzani, Rome. The study was conducted in compliance with the Declaration of Helsinki, the Good Clinical Practice guidelines, and local regulatory requirements. Before enrollment and allocation to the study arms, informed consent for participation in the study was obtained orally from all participants and a witness, present to the meeting, signed a form declaring that the patient received the cor-

rect information and gave informed consent to the participation to the trial.

Study Conduct and Oversight

The trial was designed and coordinated by the Azienda USL-IRCCS of Reggio Emilia in accordance with the protocol and its amendments. An independent data safety and monitoring committee was appointed April 29, 2020, to oversee the conduct of the trial and the safety and efficacy end points and to provide recommendations about the continuation or conclusion of the study. The Azienda USL-IRCCS of Reggio Emilia collected the data, monitored the conduct of the trial, and performed the statistical analyses.

Statistical Analysis

The study was designed to achieve an 80% power for detecting a relative reduction in the proportion of patients experiencing clinical worsening of 50% (from 20% in the control arm to 10% in the experimental arm) with a 2-sided type I error of 5%. According to these assumptions, the estimated sample size was 398 patients (199 per arm). The hypothesis of a 20% occurrence of the primary end point in the control arm was an approximation based on early data of the Reggio Emilia COVID-19 patient cohort, as well as the reduction to 10% in the treatment group.

Statistical analysis is detailed in the statistical analysis plan (Supplement 3) for primary and secondary end points. Briefly, the primary efficacy analysis was conducted on the intention-to-treat (ITT) population. The proportion of patients experiencing clinical worsening in the 2 arms during the 2 weeks following randomization was compared using the χ^2 test in an asymptotic form and the relative risk with its bilateral 95% CI. Secondary end points included the overall rate of patients admitted to the ICU with invasive mechanical ventilation at 14

Table 1. Demographic and Clinical Characteristics of Patients at Baseline

| Characteristic | No. (%) | | |
|---|----------------------|----------------------|------------------------|
| | All (n = 126) | Tocilizumab (n = 60) | Standard care (n = 66) |
| Age, median (IQR), y | 60.0 (53.0-72.0) | 61.5 (51.5-73.5) | 60.0 (54.0-69.0) |
| Sex | | | |
| Male | 77 (61.1) | 40 (66.7) | 37 (56.1) |
| Female | 49 (38.9) | 20 (33.3) | 29 (43.9) |
| Days from symptom onset to randomization, median (IQR) | 8.0 (6.0-11.0) | 7.0 (4.0-11.0) | 8.0 (6.0-11.0) |
| Days from hospital admission to randomization, median (IQR) | 2 (1-3.2) | 2 (1-3) | 2 (1-4.2) |
| Coexisting conditions | | | |
| Diabetes mellitus | 19 (15.1) | 10 (16.7) | 9 (13.6) |
| Obesity (BMI ≥ 30) ^a | 38 (32.2) | 16 (28.1) | 22 (36.1) |
| Hypertension | 56 (44.4) | 27 (45.0) | 29 (43.9) |
| COPD | 4 (3.2) | 2 (3.3) | 2 (3.0) |
| Body temperature, median (IQR), °C | 38.0 (36.9-38.5) | 38.0 (37.0-38.4) | 38.0 (36.8-38.5) |
| Respiratory rate, median (IQR), breaths/min | 20.0 (18.0-24.0) | 20.0 (18.0-24.0) | 20.0 (18.0-24.0) |
| Unknown | 13 (10.3) | 7 (11.7) | 6 (9.1) |
| C-Reactive protein, median (IQR), mg/dL | 8.2 (3.7-13.5) | 10.5 (5.0-14.6) | 6.5 (3.2-11.8) |
| White blood cell count, median (IQR), /μL | 5700 (4600-7500) | 5800 (4400-7600) | 5600 (4700-7200) |
| Unknown | 2 (1.6) | 1 (1.7) | 1 (1.5) |
| Lymphocyte count, median (IQR), /μL | 900 (700-1300) | 1000 (800-1300) | 900 (700-1200) |
| Unknown | 13 (10.3) | 8 (13.3) | 5 (7.6) |
| Platelet count, median (IQR), ×10 ³ /μL | 200.5 (158.0-253.5) | 213.0 (165.0-268.0) | 188.0 (152.0-246.0) |
| Unknown | 2 (1.6) | 1 (1.7) | 1 (1.5) |
| Pao ₂ /Fio ₂ median (IQR), mm Hg | 264.5 (243.0-290.0) | 262.5 (241.0-286.5) | 268.2 (244.0-290.0) |
| Ferritin, median (IQR), ng/mL | 569.0 (317.0-1156.0) | 646.0 (289.2-1107.5) | 533.5 (351.0-1184.0) |
| Unknown | 17 (13.5) | 9 (15.0) | 8 (12.1) |
| D-Dimer, median (IQR), μg/mL | 0.566 (0.367-0.956) | 0.756 (0.480-1.070) | 0.455 (0.326-0.810) |
| Unknown | 11 (8.7) | 6 (10.0) | 5 (7.6) |
| IL-6, median (IQR), pg/mL | 42.1 (20.6-74.9) | 50.4 (28.3-93.2) | 34.3 (19.0-59.3) |
| Unknown | 20 (15.9) | 9 (15.0) | 11 (16.7) |
| Hydroxychloroquine | 115 (91.3) | 53 (88.3) | 62 (93.9) |
| Heparin and LMWH | 81 (64.3) | 41 (68.3) | 40 (60.6) |
| Antiretrovirals ^b | 52 (41.3) | 21 (35.0) | 31 (47.0) |
| Azithromycin | 26 (20.6) | 10 (16.7) | 16 (24.2) |

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; IL-6, interleukin-6; IQR, interquartile range; LMWH, low-molecular-weight heparin; Pao₂/Fio₂, partial pressure of arterial oxygen/fraction of inspired oxygen.

^a Calculated as weight in kilograms divided by height in meters squared.

^b Antiretrovirals included darunavir/cobicistat, darunavir/ritonavir, or

lopinavir/ritonavir. No remdesivir was administered.

SI conversion factors: To convert C-reactive protein to mg/L, multiply by 10; D-dimer to nmol/L, multiply by 5.476; ferritin to μg/L, multiply by 1.0; lymphocyte count to ×10⁹/L, multiply by 0.001; platelet count to ×10⁹/L, multiply by 1.0; white blood cell count to ×10⁹/L, multiply by 0.001.

and 30 days. They were analyzed as stated for the primary end point. We reported the *P* value only for the primary efficacy analysis (2-tailed; significance defined as *P* ≤ .05), and bilateral 95% CI not adjusted for multiplicity for all the other comparisons. Statistical analyses were performed with SAS, version 9.4 (SAS Institute) and SPSS, version 23 (IBM Corp).

The original protocol did not include any interim analysis. On April 24, 2020, the AIFA, the authority responsible for drug regulation in Italy, observing the low rate of recruitment in all COVID-19 Italian trials, suggested the possibility of introducing interim analyses in ongoing trials. The trial scientific committee discussed this hypothesis on April 30 with the independent data safety and monitoring committee, which proposed an interim analysis for futility at one-third of the planned sample size (132 patients). A formal amendment was submitted to the Ethics Committee on May 18. In the meantime, the enrollment had virtually ceased, mainly because of the dramatic decrease

in the incidence of the disease, and on June 2, the statistical report was sent to the data safety and monitoring committee, based on 124 patients with at least 2 weeks of follow-up: the estimated conditional power was less than 1% under the null and less than 57% under the alternative hypothesis. On June 11, 2020, the trial Scientific Committee decided to interrupt the study for futility with an enrollment of 126 patients.

Results

Patients

A total of 126 patients with COVID-19 pneumonia were included in this analysis. Demographic and baseline clinical characteristics are summarized in Table 1. The majority of patients were male (61.1%) with a median (range) age of 60.0 (53.0-72.0) years. Of the 126 enrolled patients, 3 patients, all

Table 2. Clinical Outcomes in the Intention-to-Treat Population

| Outcome | No. (%) | | Rate ratio (95% CI) | P value |
|---------------------------------|----------------------|------------------------|---------------------|---------|
| | Tocilizumab (n = 60) | Standard care (n = 63) | | |
| Primary end point at 14 d | | | | |
| Clinical worsening ^a | 17 (28.3) | 17 (27.0) | 1.05 (0.59-1.86) | .87 |
| Overall events at 14 d | | | | |
| Admissions to ICU | 6 (10.0) | 5 (7.9) | 1.26 (0.41-3.91) | |
| Deaths | 1 (1.7) | 1 (1.6) | 1.05 (0.07-16.4) | |
| Discharges | 34 (56.7) | 36 (57.1) | 0.99 (0.73-1.35) | |
| Overall events at 30 d | | | | |
| Admissions to ICU | 6 (10.0) | 5 (7.9) | 1.26 (0.41-3.91) | |
| Deaths | 2 (3.3) | 1 (1.6) | 2.10 (0.20-22.6) | |
| Discharges | 54 (90.0) | 58 (92.1) | 0.98 (0.87-1.09) | |

Abbreviations: ICU, intensive care unit; PaO₂/FIO₂, partial pressure of arterial oxygen/fraction of inspired oxygen.

^a One patient in the standard care group was admitted to the ICU without a PaO₂/FIO₂ ratio less than 150 mm Hg.

allocated to the standard care arm, withdrew consent at days 2, 3, and 6. Their PaO₂/FIO₂ ratios measured the day they opted out were 281, 232, and 318 mm Hg, respectively. Therefore, 123 patients were included in the ITT analysis; 60 were randomized to receive tocilizumab at enrollment, and 63 were randomized to standard care until clinical worsening (Figure 1). Two patients (1 per arm) were enrolled in the study while having exclusion criteria at baseline: 1 was on noninvasive ventilation, and 1 had diverticulitis.

A total of 59 patients (98.3%) randomized in the tocilizumab arm received the treatment after randomization according to the protocol schedule. One did not receive tocilizumab because gastrointestinal bleeding occurred just after randomization. The event was reported as a serious adverse event. One patient received steroids on day 4 after a PaO₂/FIO₂ ratio less than 150 mm Hg not confirmed by a second measurement.

In the standard care arm, 2 patients received tocilizumab IV plus steroids before the documented clinical worsening, after PaO₂/FIO₂ ratio measurements of 169 and 426 mm Hg, respectively, and 1 received tocilizumab subcutaneously after a PaO₂/FIO₂ ratio measurement of 192 mm Hg. Two received steroids after a PaO₂/FIO₂ ratio measurement of 200 and 229 mm Hg, and 1 received canakinumab after a PaO₂/FIO₂ ratio measurement of 210 mm Hg. Overall, 8 patients did not receive the treatment according to the protocol (6 in the control arm and 2 in the experimental arm), and 2 noneligible patients were excluded from the analyses per protocol; thus, the population for protocol analysis was 113 patients (see eResults in Supplement 1 for more details).

Fourteen patients in the standard care arm received tocilizumab IV, including 2 who received tocilizumab and steroids, after clinical worsening (Figure 1). All patients were followed for 14 days according to the study protocol and for at least 30 days for secondary end points (admissions to ICU and mortality). Patients were randomized after a median (interquartile range) time from symptom onset of 8 (6-11) days. No patient received glucocorticoids before enrollment.

Primary Outcome

Seventeen patients of 60 (28.3%) in the tocilizumab arm and 17 of 63 (27.0%) in the standard care group showed clinical

worsening within 14 days since randomization (rate ratio, 1.05; 95% CI, 0.59-1.86; *P* = .87) (Table 2; eTable 1 in Supplement 1). All 34 episodes of clinical worsening occurred within 6 days after randomization (Figure 2), with no differences in time to the event between the 2 arms. These included 33 patients who had a PaO₂/FIO₂ ratio less than 150 mm Hg and 1 patient who was admitted to ICU without a PaO₂/FIO₂ ratio less than 150 mm Hg. For 21 of 33 patients, the outcome was identified through a double measurement of PaO₂/FIO₂ ratio less than 150 mm Hg, with the second one performed within 4 hours. For 5 patients, the second measurement was performed within the same day. For 7 patients, it was not possible to perform a second assessment the same day.

Secondary Outcomes

Eleven patients were admitted to ICU, all within 14 days since randomization, with no major differences between the 2 arms (10.0% vs 7.9%, respectively). The rate ratio was 1.26 (95% CI, 0.41-3.91) (Table 2).

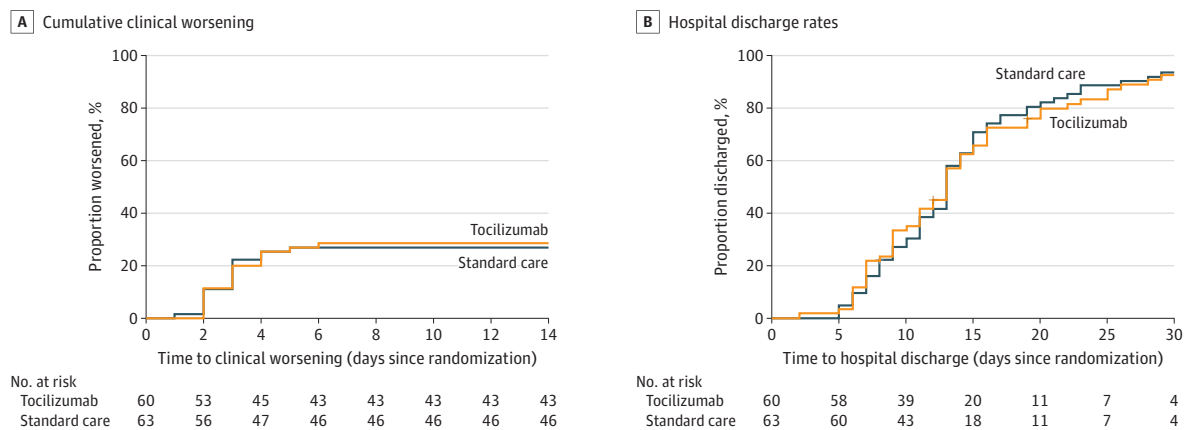
Four deaths occurred in this population, 2 within 14 days (1 in the tocilizumab arm and 1 in the standard care arm, 12 and 8 days since randomization) and 1 between day 15 and day 30 (in the tocilizumab arm, 19 days since randomization) (Table 2). One event occurred 36 days since randomization in the tocilizumab arm. Mortality at 14 days (1.7% vs 1.6%; rate ratio, 1.05; 95% CI, 0.07-16.4) and at 30 days (3.3% vs 1.6%; rate ratio, 2.10; 95% CI, 0.20-22.6) was comparable in the 2 groups.

A total of 117 of 123 patients (95.1%) were discharged from hospital, 70 (56.9%) within 14 days and 112 (91.1%) within 30 days. Two patients were still in hospital (one in ICU) after 61 and 68 days since randomization. The proportion of patients discharged within 14 and 30 days (Table 2) was the same in the 2 groups (rate ratio, 0.99; 95% CI, 0.73-1.35; and 0.98; 95% CI, 0.87-1.09; respectively). No difference in PaO₂/FIO₂ ratio and lymphocyte count was observed in the 2 groups at 14 days (eFigure in Supplement 1).

Per-Protocol Analysis

Results are detailed in eTable 2 in Supplement 1. In the population of 113 patients, the results confirmed those observed in the ITT analyses.

Figure 2. Kaplan-Meier Estimates of Cumulative Clinical Worsening and Hospital Discharge



Kaplan-Meier estimates of cumulative clinical worsening (A) and hospital discharge (B).

Table 3. Adverse Events by System Organ Class and Treatment Arm

| MedDRA system organ class | Adverse events, No. (%) | | |
|---|-------------------------|----------------------|------------------------|
| | Total (n = 123) | Tocilizumab (n = 60) | Standard care (n = 63) |
| Any system ^a | 21 (17.1) | 14 (23.3) | 7 (11.1) |
| Gastrointestinal disorders | 2 (1.6) | 1 (1.7) | 1 (1.6) |
| Infections and infestations ^b | 5 (4.1) | 1 (1.7) | 4 (6.3) |
| Injury, poisonings, and procedural complications ^c | 1 (0.8) | 1 (1.7) | 0 |
| Laboratory abnormalities ^d | 10 (8.1) | 8 (13.3) | 2 (3.2) |
| Metabolism ^e | 2 (1.6) | 2 (3.3) | 0 |
| Vascular disorders | 1 (0.8) | 1 (1.7) | 0 |

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.

^a One patient had 2 events (tocilizumab group), and 1 patient had 3 events (standard care group).

^b Urinary tract infection (1 in tocilizumab group); sepsis (2 in standard care group); esophageal infection (1 in standard care group); bronchial infection (1 in standard care group).

^c Fall.

^d Increased alanine aminotransferase (2 in standard care group: 1 mild, 1 moderate; 5 in tocilizumab group: 2 mild, 2 moderate, 1 severe); decreased neutrophil count (3 in tocilizumab group: 1 mild, 2 moderate).

^e One had hyperglycemia; 1 had hypokalemia.

Safety Outcomes

Serious adverse events occurred in 3 patients: 2 severe infections (standard care) and 1 upper gastrointestinal tract bleeding (experimental) that prevented the treatment administration (Table 3). None were considered to be treatment related by site investigators. There were 21 (17.1%) adverse events, 14 (23.3%) in the tocilizumab group and 7 (11.1%) in the standard care group. The most common adverse events were increased alanine aminotransferase level and decreased neutrophil count.

Discussion

Observational studies have suggested that tocilizumab is effective in reducing mortality and/or intubation in patients with severe COVID-19 pneumonia.¹³⁻¹⁷ Those promising results led to this randomized clinical trial, which suggests that tocilizumab, administered early in hospitalized patients with COVID-19 pneumonia, provides no advantage over standard supportive care. Our study considered patients with mild acute

respiratory distress syndrome ($\text{PaO}_2/\text{FIO}_2$ ratio between 200 and 300 mm Hg) and inflammatory response characterized either by elevated CRP levels or fever with temperature greater than 38 °C for 2 days.

In the ITT analysis, no significant differences were observed in the occurrence of the primary composite end point between the experimental and the control groups at 14 days (28.3% in the experimental group vs 27.0% in the control group). Similar results were shown in the per-protocol analysis. Furthermore, no difference between the study groups was observed for any of the 3 outcomes composing the primary end point, including the proportion of patients admitted to an ICU or the overall mortality. These findings were also similar at 30 days from randomization.

Notably, our study has a low lethality, with 1 (0.8%) deceased patient at 14 days and 2 more (2.4% overall) at 30 days of follow-up in the 123 patients included in the ITT population. This can have several and possibly concurring explanations. First, we excluded patients not eligible for a future admission to the ICU regardless of the evolution of the clinical condition because of a preexisting condition or because the

patient expressed a specific will. The ICU eligibility criteria were not specified in the protocol, as they varied according to different centers' situations, which can change during the pandemic. Consequently, this might have excluded older adult patients and those with comorbidities at higher risk of mortality. Second, patients with a $\text{PaO}_2/\text{FIO}_2$ ratio below 200 mm Hg were not eligible, as we wanted to assess tocilizumab efficacy in patients with less severe disease. For these reasons, the baseline conditions of our population were likely better than those of the whole population of hospitalized patients with COVID-19. Of interest, our study confirmed the safety profile of tocilizumab in patients with COVID-19, with 2 severe adverse events after tocilizumab treatment.

Limitations

Our trial has several limitations, but also some strengths. Among the limitations is that the trial was open label. The possibility of conducting a double-blind placebo-controlled trial was considered, but it was excluded for 2 main reasons: the logistic obstacles in organizing it in a period of emergency and the intrinsic anti-IL-6 effect of tocilizumab. It has been consistently reported and clinically observed that this monoclonal antibody rapidly lowers fever and serum CRP level in patients with COVID-19,^{14,18} thus making allocation concealment unlikely. In addition, as 14 patients in the control group received tocilizumab after they reached the primary end point, subsequent secondary outcomes might be affected. The decision to allow a rescue therapy with tocilizumab was motivated by ethical concerns regarding the use of a safe and potentially effective drug as reported by previous retrospective studies. Nevertheless, rescue therapy did not influence the primary outcome based on the per-protocol analysis. Yet, one may speculate that lack of blinding could have caused a bias in the assessment of the primary end point. To this regard, 2 considerations can be made. First, and most important, any bias in the assessment of the primary end point due to the knowledge of the treatment arm was more likely to favor the experimental arm because tocilizumab could be offered to patients in the control arm once the primary end point had been reached. Theoretically, investigators could be more inclined to classify a patient as clinically worsened in the control arm than in the experimental arm. Although this bias seems unlikely to be a plausible cause of the negative results of this trial, we cannot exclude that investigators who doubt the efficacy of tocilizumab would have been inclined to classify a patient in the experimental arm as clinically worsened, thus favoring the control arm. Second, most instances of clinical worsening (33 of 34) were due to the occurrence of a reduced $\text{PaO}_2/\text{FIO}_2$ ratio, which, as defined in the composite primary outcome definition, can be hardly influenced by knowledge of the treatment.

Patients in the control arm had lower CRP, IL-6, ferritin, and D-dimer levels and were more frequently treated with an-

tivirals compared with patients in the tocilizumab group at baseline, despite randomization. This may have led to bias toward the null. However, these differences were not statistically significant, and the differences between the single values were small. We believe that these differences are due to the limited sample size, as allocation concealment was based on a centralized randomization list that was not available to clinicians. Furthermore, obesity was less frequent in the experimental group, and age was similar in the 2 groups, thus making a bias toward the null unlikely.

Because of the selection criteria and the primary end point of this study, the results do not allow ruling out the possible role of tocilizumab in reducing the risk of death or intubation in patients presenting with more advanced disease. We considered a composite primary end point that was defined by the event of either death, intubation, or a respiratory worsening with $\text{PaO}_2/\text{FIO}_2$ less than 150 mm Hg, whichever occurred first. However, of the 34 patients reaching the primary end point, all but 1 reached it because of a $\text{PaO}_2/\text{FIO}_2$ less than 150 mm Hg. Among the 17 patients reaching the primary end point in the standard care group, 14 received tocilizumab as a rescue therapy. At 30 days, the incidence of intubation and death was comparable between the 2 groups. Therefore, we cannot exclude that tocilizumab is effective in preventing death or intubation at 30 days independently to administration timing. However, we can infer that the early administration of this drug in patients with COVID-19 pneumonia does not provide any significant advantage in reduction of intubation or mortality compared with a deferred administration with a $\text{PaO}_2/\text{FIO}_2$ ratio less than 150 mm Hg.

To our knowledge, this is the first randomized clinical trial evaluating the efficacy and safety of tocilizumab in patients with COVID-19 pneumonia. Even though we did not have an exaggerated inflammatory response, our study population had elevated CRP levels at baseline and fever, suggesting the presence of a vigorous inflammation at enrollment. Moreover, the median time from symptom onset to enrollment was 8 days, consistent with the findings that hyperinflammatory response and hospital admission generally occur 1 week after the earliest manifestations.^{2,4,19,20}

Conclusions

The administration of tocilizumab in patients with COVID-19 pneumonia and a $\text{PaO}_2/\text{FIO}_2$ ratio between 200 and 300 mm Hg did not reduce the risk of clinical worsening. Further blinded, placebo-controlled randomized clinical trials are needed to confirm the results and to explore possible applications of tocilizumab in different stages of the disease, such as in patients with a $\text{PaO}_2/\text{FIO}_2$ ratio less than 200 mm Hg.

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