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Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia
A Randomized Clinical Trial

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IMPORTANCE Severe pneumonia with hyperinflammation and elevated interleukin-6 is a common presentation of coronavirus disease 2019 (COVID-19).

OBJECTIVE To determine whether tocilizumab (TCZ) improves outcomes of patients hospitalized with moderate-to-severe COVID-19 pneumonia.

DESIGN, SETTING, AND PARTICPANTS This cohort-embedded, investigator-initiated, multicenter, open-label, bayesian randomized clinical trial investigating patients with COVID-19 and moderate or severe pneumonia requiring at least 3 L/min of oxygen but without ventilation or admission to the intensive care unit was conducted between March 31, 2020, to April 18, 2020, with follow-up through 28 days. Patients were recruited from 9 university hospitals in France. Analyses were performed on an intention-to-treat basis with no correction for multiplicity for secondary outcomes.

INTERVENTIONS Patients were randomly assigned to receive TCZ, 8 mg/kg, intravenously plus usual care on day 1 and on day 3 if clinically indicated (TCZ group) or to receive usual care alone (UC group). Usual care included antibiotic agents, antiviral agents, corticosteroids, vasopressor support, and anticoagulants.

MAIN OUTCOMES AND MEASURES Primary outcomes were scores higher than 5 on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS) on day 4 and survival without need of ventilation (including noninvasive ventilation) at day 14. Secondary outcomes were clinical status assessed with the WHO-CPS scores at day 7 and day 14, overall survival, time to discharge, time to oxygen supply independency, biological factors such as C-reactive protein level, and adverse events.

RESULTS Of 131 patients, 64 patients were randomly assigned to the TCZ group and 67 to UC group; 1 patient in the TCZ group withdrew consent and was not included in the analysis. Of the 130 patients, 42 were women (32%), and median (interquartile range) age was 64 (57.1-74.3) years. In the TCZ group, 12 patients had a WHO-CPS score greater than 5 at day 4 vs 19 in the UC group (median posterior absolute risk difference [ARD] −9.0%; 90% credible interval [CrI], −21.0 to 3.1), with a posterior probability of negative ARD of 89.0% not achieving the 95% predefined efficacy threshold. At day 14, 12% (95% CI −28% to 4%) fewer patients needed noninvasive ventilation (NIV) or mechanical ventilation (MV) or died in the TCZ group than in the UC group (24% vs 36%, median posterior hazard ratio [HR] 0.58; 90% CrI, 0.33-1.00), with a posterior probability of HR less than 1 of 95.0%, achieving the predefined efficacy threshold. The HR for MV or death was 0.58 (90% CrI, 0.30 to 1.09). At day 28, 7 patients had died in the TCZ group and 8 in the UC group (adjusted HR, 0.92; 95% CI 0.33-2.53). Serious adverse events occurred in 20 (32%) patients in the TCZ group and 29 (43%) in the UC group (P = .21).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial of patients with COVID-19 and pneumonia requiring oxygen support but not admitted to the intensive care unit, TCZ did not reduce WHO-CPS scores lower than 5 at day 4 but might have reduced the risk of NIV, MV, or death by day 14. No difference on day 28 mortality was found. Further studies are necessary for confirming these preliminary results.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04331808

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Group Information: The members of the CORIMUNO-19 Collaborative Group appear in Supplement 1.

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Coronavirus disease 2019 (COVID-19) is a respiratory disease induced by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) causing substantial morbidity and mortality.[1-4] Most people with COVID-19 have only mild or uncomplicated symptoms, but approximately 10% to 15% have moderate or severe disease that requires hospitalization and oxygen support, and 3% to 5% require admission to an intensive care unit (ICU).[5] In severe cases, COVID-19 can be complicated by acute respiratory distress syndrome (ARDS). Older age, male sex, and comorbid diseases are risk factors for death.[6-8]

A previous trial showed that the antiviral agent remdesivir reduced the length of recovery by 4 days but did not reduce the number of patients needing mechanical ventilation (MV), nor the death rate.[9] In addition, the RECOVERY collaborative group demonstrated that dexamethasone (DXM) 6 mg/d for 10 days decreased the 28-day mortality among patients receiving MV or oxygen.[10]

At the beginning of the epidemic in France, when no standard of care was defined, we decided to set up the publicly supported CORIMUNO-19 platform dedicated to perform cohort, open-label, randomized controlled trials of immune modulatory drugs in hospitalized patients with moderate or severe COVID-19. The overall objective was to explore several immune modulatory drugs to design larger trials to confirm the best drug in a defined population of patients with severe COVID-19 pneumonia and eventually new standard of care.

Patients with severe COVID-19 pneumonia present nonspecific inflammatory responses, including edema and inflammatory cell infiltration in the lungs. Besides the specific pathogenic effect of SARS-CoV-2, this deleterious excessive and noneffective host immune response plays an important role during the disease course. It is related to a hyperinflammatory status comprising a number of proinflammatory cytokines and chemokines, one of the most predominant being bx;1interleukin 6 (IL-6).[11,12]

Given the potential deleterious effect of IL-6 in COVID-19 pneumonia,[13-15] we first evaluated the benefit-risk effect of tocilizumab (TCZ), an anti–human IL-6 receptor (IL-6R) monoclonal antibody that inhibits IL-6 signaling by binding soluble IL-6R and membrane IL-6R and is approved for rheumatoid arthritis, juvenile inflammatory arthritis and refractory giant cell arteritis. Tocilizumab is also approved for systemic inflammatory response caused by the massive release of proinflammatory cytokines in response to iatrogenic disease (eg, chimeric antigen receptor T-cell therapies). Preliminary data from observational studies suggested the possible efficacy of TCZ for moderate, severe, or critical COVID-19[16-18] but, until now, no data are available from randomized clinical trials. We set up this multicenter randomized clinical trial assessing the ability of TCZ to improve the outcome of patients hospitalized with moderate-to-severe COVID-19 pneumonia.

Key Points

Question What is the effect of tocilizumab, an anti–interleukin-6 receptor antibody, in patients with COVID-19 and moderate-to-severe pneumonia?

Findings In this randomized clinical trial that included 130 patients hospitalized with COVID-19 and moderate-to-severe pneumonia, tocilizumab did not reduce the World Health Organization 10-point Clinical Progression Scale scores lower than 5 at day 4, and the proportion of patients with noninvasive ventilation, intubation, or death at day 14 was 36% with usual care and 24% with tocilizumab. No difference in mortality over 28 days was found between the 2 groups.

Meaning Tocilizumab may reduce the need for mechanical and noninvasive ventilation or death by day 14 but not mortality by day 28; further studies are necessary to confirm these preliminary results.

Methods

Trial Design and Study Oversight

The trial protocol is available in Supplement 2. We enrolled patients with COVID-19 to perform a series of randomized clinical trials testing different therapeutic regimens (CORIMUNO-19 Cohort). Two separate populations were recruited: patients with moderate or severe pneumonia and patients with critical pneumonia. An institutional review board-approved amendment to the protocol on April 6, 2020, clarified the definition of these 2 populations as follows (eMethods in Supplement 3): (1) patients with moderate or severe pneumonia and with WHO 10-point Clinical Progression Scale (WHO-CPS) score of 5 receiving at least 3L/min oxygen (O_2) but without high-flow oxygen (HFO) (defined by using Optiflow device with more than 15 L/min O_2), noninvasive ventilation (NIV) or mechanical ventilation (MV) and (2) patients with critical pneumonia defined as WHO-CPS score of 6 or more (ie, with HFO, NIV, or MV).

This article reports on CORIMUNO-TOCI 1, a CORIMUNO, multicenter, open-label, randomized clinical trial in patients with moderate or severe pneumonia. The trial registration, NCT04331808, describes this study and a second study, CORIMUNO-TOCI 2, a trial conducted in patients with critical pneumonia. Although the 2 trials were placed under the same registration number, they are distinct studies with different participants, and were never intended to be reported together.

Accrual for this study took place in 9 French university hospitals. Because of the emergency nature of the trial and feasibility issues, no placebo of TCZ was prepared.

The CORIMUNO Cohort and all embedded trials (ie, trials using data collected in the CORIMUNO cohort) were approved by an ethics committee (CPP Île-de-France VI) and relevant authorities. Legal issues and trial procedures are presented in detail in the eMethods in Supplement 3. Written informed consent was obtained from all patients or from the patient's legal representative for entering the CORIMUNO cohort, and longitudinal data (including clinical status, biological data and outcomes) were recorded as part of their participation in the cohort. In this consent, patients were made aware that a number of trials may occur via the cohort, and that they would likely be offered to participate in some of them. In practice, for logistical reasons, only 1 trial took place at each site at a given time. A specific additional written consent was obtained from eligible patients who were randomly selected to

be offered TCZ and agreed to receive this treatment. Eligible patients assigned to receive usual care (UC) were not notified about the trial, but their CORIMUNO-cohort data were available for analysis. An amendment to the protocol on April 6, 2020, modifying inclusion criteria and the late primary outcome is described in the eMethods 2.5 in Supplement 3. A data safety monitoring board (DSMB) was set up at the beginning of the study and resigned on April 30, 2020, because of differences between the investigators and sponsors and the DSMB with regard to the management of the protocol and the communication of the results. No issues of participant safety or data integrity were raised. A new DSMB was appointed on May 1, 2020, which was approved by the Agence Nationale de Sécurité du Médicament et des Produits de Santé on May 3, 2020.

This trial was reported according to Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Patients

Patients were included in the CORIMUNO-19 cohort if they had confirmed SARS-CoV-2 infection (positive on rRT-PCR and/or typical chest computed tomographic [CT] scan) with moderate, severe, or critical pneumonia (O_2 >3 L/min, WHO Clinical Progression Scale [WHO-CPS] score ≥5[19] [10-point ordinal scale described in the eMethods 2.4 in Supplement 3]).

Patients from the CORIMUNO-19 cohort were eligible for CORIMUNO-TOCI-1 trial if they had a WHO-CPS score of 5 with O_2 levels of 3 L/min or higher but without noninvasive ventilation (NIV) or mechanical ventilation (MV). Exclusion criteria are detailed in the eMethods in Supplement 3.

Randomization and Treatments

Participants were randomly assigned in a 1:1 ratio to receive TCZ plus usual care (TCZ group) or usual care alone (UC group) via a web-based secure centralized system. An independent statistician provided a computer-generated assignment randomization list stratified by center and blocked with varying block sizes unknown to the investigators.

Tocilizumab was administered intravenously (IV) at 8 mg/kg on day 1. Administration of an additional fixed dose of TCZ, 400 mg IV, on day 3 was recommended if oxygen requirement was not decreased by more than 50%, but decision was left to the treating physician. Usual care (antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants) was provided at the discretion of the clinicians.

Outcome Measures

The 2 primary outcomes were (1) the proportion of patients dead or needing noninvasive or mechanical ventilation on day 4 (>5 on the WHO-CPS); and (2) survival with no need for noninvasive or mechanical ventilation at day 14. The day 4 and 14 outcomes were amended on April 6, 2020, to include high-flow oxygen in noninvasive ventilation to be consistent with the WHO-CPS definition. Both outcomes were consistent with the core outcome set proposed by the WHO[19] (eMethods 2.4 in Supplement 3). Prespecified secondary outcomes were clinical status assessed with the WHO-CPS at day 7 and day 14, overall survival, time to discharge, and time to oxygen supply independency. We also measured biological factors such as C-reactive protein levels and adverse events.

Data Quality Monitoring

Data quality monitoring included both remote data monitoring and on-site monitoring performed by dedicated staff independent of the site investigators, with 100% source data verification performed for all patients recruited at every site for all critical data points.

Statistical Analysis

To maximize information from limited data generated while allowing for a rapid decision, we used a bayesian monitoring and analysis of the trial based on the coprimary outcomes. The sample size was set at 120, with interim analyses presented weekly to the DSMB and a provision to increase the sample size in case of promising but not conclusive results. We computed that the trial would have frequentist power of 97.2% to detect a decrease in event rate from 0.50 to 0.20, and 73.9% to detect a decrease in event rates from 0.50 to 0.30. For the day 4 outcome, we used a beta prior distribution with parameters 1 and 1 for the proportion in each arm (eFigure 1 in Supplement 3). For the day 14 outcome, we used a Gaussian prior distribution with a mean of 0 and variance of 10^6 for the log hazard ratio (HR) (eTable 1 in Supplement 3). Sensitivity analyses using a range of prior distribution were then conducted (eMethods, eFigure 2 in Supplement 3). The treatment effect was expressed in terms of absolute risk difference (ARD) for the day 4 outcome and HR for the day 14 outcome. Using Markov chain Monte Carlo methods, posterior probabilities of negative ARD and HR less than 1 were computed. According to the protocol, posterior probability greater than 0.99 at the interim analysis or greater than 0.95 at the final analysis indicated efficacy. We also computed posterior probability of ARD less than −5.5% and HR less than 0.85 (denoting moderate or greater effect). Because the decision rules are 1-sided, consistent credible intervals (CrIs) would be theoretical. However, we chose to report 2-sided 90% CrIs, which have the same upper bound as 1-sided 95% CrIs. A subgroup analysis according to antiviral drug use at baseline was prespecified in the protocol. Analyses according to the use of corticosteroids or DXM were added post-hoc in light of recent publications. Secondary outcomes were analyzed in a frequentist framework, except the analysis of the WHO-CPS scores as an ordinal variable. The Statistical Analysis Plan and details of the statistical analyses are in Supplement 2.

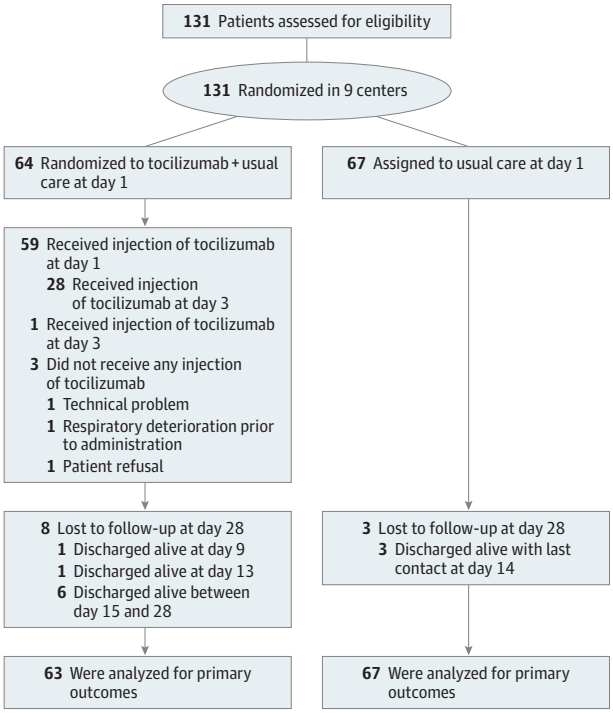
Analyses were performed on an intention-to-treat basis with no correction for multiplicity for secondary outcomes. Thus, these results are exploratory and reported as point estimates and 95% confidence intervals (CIs). Statistical analyses involved using SAS (version 9.4, SAS Institute) and R (version 3.6.1, R Foundation) statistical software.

Results

Patients

From March 31 to April 18, 2020, 131 patients were randomized (64 patients to the TCZ group and 67 to the UC group), and

Figure 1. Study Flowchart[a]



[a] One patient withdrew consent and asked data to be erased. According to European regulation, no data were analyzed for this patient.

the DSMB did not advise further increasing the sample size. Among the 64 patients assigned to receive TCZ, 1 withdrew consent and was not analyzed, and 3 did not receive TCZ because of death (n = 1), technical problems (n = 1), and patient refusal (n = 1). Among the 60 with TCZ treatment, 28 (47%) received a second injection on day 3 (**Figure 1**). Demographic and baseline clinical and biological characteristics of patients are described in **Table 1**. The median age was 64 years (interquartile range, 57.1 to 74.3 years), and 88 (68%) were men. There were no important between-group differences at enrollment.

During the trial, antiviral drugs, glucocorticoids, and preventive or therapeutic anticoagulants were administered in 7 (11%), 21 (33%), and 59 (94%) patients, respectively, in the TCZ group, and 16 (24%), 41 (61%), and 61 (91%) in the UC group, respectively. Additional immunomodulators were administered to 1 patient in the TCZ group (anakinra) and 4 in the UC group (anakinra, n = 3; eculizumab, n = 1). The details of the treatments received at the time of and after randomization until day 14 are summarized in eTable 2 in Supplement 3.

Primary Outcomes

On day 4, 12 of 63 (19%) patients randomized to receive TCZ had a WHO-CPS score higher than 5 vs 19 of 67 (28%) in the UC group (median posterior ARD, −9%; 90% CrI, -21 to 3) (eTable 3 in Supplement 3). The posterior probability of negative ARD (TCZ better than UC) was 89.0% and ARD less than −5.5% was 68.4%.

On day 14, at least 1 event (NIV, HFO, MV, or death) had occurred in 15 patients in the TCZ group (24%) (cumulative incidence of event 24%; 95% CI, 13% to 35%) and 24 patients in the UC group (cumulative incidence 36%; 95% CI, 33%-58%) (**Figure 2**A; **Table 2**; eTable 4 in Supplement 3). The posterior probability of any efficacy of TCZ (HR<1) was 95.0%, and of moderate or greater efficacy (HR<0.85) was 87.4% (posterior median HR, 0.58; 90% CrI, 0.33-1.00) (eTable 5 in Supplement 3). Results on both primary outcomes were similar in the subgroup of patients with rRT-PCR-confirmed SARS-CoV-2 infection (eTable 6 in Supplement 3).

The number of patients with MV or death at Day 14 was 11 (17%) and 18 (27%) in the TCZ and UC groups. The posterior probability of HR less than 1 and HR less than 0.85 was 92.5% and 84.4%, respectively (posterior median HR, 0.58; 90% CrI, 0.30-1.09) (Figure 2B).

On prespecified (for antiviral drugs) or post-hoc subgroup analyses (for corticosteroids, including DXM), the effect of TCZ was numerically higher if combined with antiviral drugs (HR, 0.28; 90% CrI, 0.07-1.06) or corticosteroids (HR, 0.38; 90% CrI, 0.13-1.11) (eFigure 3 in Supplement 3).

Secondary Outcomes

The evolution of WHO scores during 14-day follow-up is given eFigure 4 and eTable 7 in Supplement 3. Among patients who were not in ICU at randomization, 11 of 60 (18%) in the TCZ group and 22 of 64 (36%) in the UC group were subsequently admitted to the ICU (risk difference, 18%; 95% CI, 0.4%-31%, this analysis was unplanned). At day 28, 7 patients had died in the TCZ group and 8 in the UC group (adjusted HR, 0.92; 95% CI, 0.33-2.53) (Figure 2C; **Table 3**; eTable 8 in Supplement 3). Overall, with a median follow-up of 28 days, 7 deaths (all from ARDS) occurred in the TCZ group and 11 (ARDS, n = 9; multiorgan failure, n = 1; pulmonary embolism, n = 1) in the UC group. Of note, 3 deaths occurred after day 28 in the UC group. Causes of death are shown in Table 3.

The cumulative incidence of patients who have been weaned from oxygen at day 28 was 89% (95% CI, 78%-95%) and 75% (95% CI, 62%-83%) in the TCZ and UC group, respectively (HR, 1.41; 95% CI, 0.98-2.01) (eTable 9 in Supplement 3). The cumulative incidence of discharge by day 28 was 83% (95% CI, 70%-90%) and 73% (95% CI, 61%-82%), respectively (HR, 1.52; 95% CI, 1.02-2.27) (eTable 9 in Supplement 3).

Biological Response

C-reactive protein level and neutrophil count decrease was rapid in the TCZ arm, and lymphocyte count was increased (eFigure 5 in Supplement 3). No patient in the TCZ group remained with high C-reactive protein level after day 4.

Safety

A total of 28 (44%) and 36 (54%) patients in the TCZ and UC groups reported adverse events between randomization and day 28 (Table 3). Serious adverse events occurred in 20 (32%) in the TCZ group and 29 (43%) in the UC group (P = .21). The number of serious adverse events was lower in the TCZ than UC group (27 vs 57) with a decreased incidence of serious bacterial infections (2 vs 11).

Table 1. Patient Characteristics at Baseline

Characteristic	No.	Tocilizumab, No./No. (%)	No.	UC, No./No. (%)
No.		63		67
Age, median (IQR), y		64.0 (57.1-74.3)		63.3 (57.1-72.3)
Male		44/63 (70)		44/67 (66)
Female		19/63 (30)		23/67 (34)
Weight, median (IQR), kg		80.0 (70.0-90.0)	55	78.0 (70.0-90.0)
BMI,[a] median (IQR)	46	27.9 (23.3-30.8)	46	27.4 (24.5-31.3)
WHO-CPS score (0-10) = 5		63/63 (100)		67/67 (100)
rRT-PCR–confirmed SARS-CoV-2 infection		56/63 (89)		61/67 (90)
Temperature, median (IQR), °C		37.3 (36.8-38.2)		37.9 (37.0-38.6)
Respiratory rate, median (IQR), bpm	56	24.0 (22.0-30.0)	57	26.0 (24.0-30.0)
Flow, median (IQR), L/min		5.0 (3.0-8.0)		5.0 (3.0-6.0)
SpO_2, median (IQR), %		95.0 (93.0-96.0)		95.0 (93.0-97.0)
Time from symptoms onset to randomization, median (IQR), d	62	10 (7-13)	66	10 (8-13)
Time from hospital admission to randomization, median (IQR), d	63	1 (1-4)	67	1 (1-2)
Coexisting conditions				
Chronic cardiac disease		20/61 (33)		20/67 (30.0)
Diabetes		20/61 (33)		23/67 (34)
Chronic kidney disease (stage 1 to 3) or dialysis		5/61 (8)		13/67 (19)
Asthma		5/61 (8)		3/67 (5)
Chronic pulmonary disease (not asthma)		3/61 (5)		3/67 (5)
Active malignant neoplasm		4/61 (7)		5/67 (8)
Smoking				
No		55/61 (90)		62/67 (93)
Current		1/61 (2)		2/67 (3)
Former		5/61 (8)		3/67 (4)
Laboratory values, median (IQR)				
CRP, mg/L	56	119.5 (74.5-219.5)	63	127.0 (84.0-171.0)
D-Dimer, µg/L	50	869 (524-1380)	50	1250 (780-1812)
Neutrophil count, G/L	60	4.9 (3.9-7.5)	63	5.1 (3.4-6.6)
Lymphocyte count, G/L	60	1.0 (0.7-1.4)	60	1.1 (0.6-1.2)
Lymphocytes to neutrophils ratio	48	0.2 (0.1-0.3)	40	0.2 (0.1-0.3)
Hemoglobin, g/dL	62	12.8 (11.9-13.8)	65	12.3 (10.9-13.4)
Platelet count, g/L	62	230 (187-324)	65	226 (163-286)
ALT/SGPT, IU/L	57	40.0 (30.0-67.0)	62	35.0 (22.0-55.0)
AST/SGOT, IU/L	58	50.0 (34.0-66.0)	62	55.0 (36.0-74.0)
Albumin, g/L	43	30.0 (27.0-36.0)	42	32.2 (28.0-36.0)
Creatinine, µmol/L	61	71.0 (56.0-87.0)	64	75.0 (59.5-119.5)
Blood urea, mmol/L	62	5.8 (4.4-7.7)	65	5.1 (4.2-8.6)
Ferritin, mg/L	43	1292 (424-2484)	46	1070 (563-1790)
LDH, IU/L	46	401 (313-582)	51	434 (351-558)
CPK, IU/L	42	136.0 (48.0-284.0)	41	105.0 (67.0-236.0)

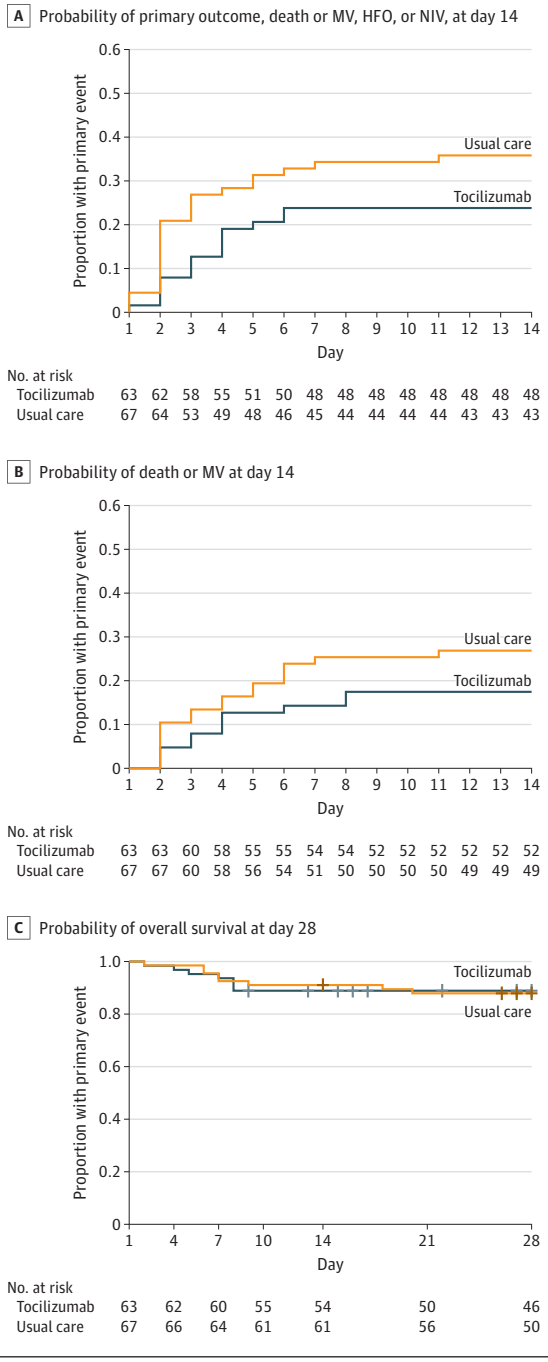
Abbreviations: ALD, alanine aminotransferase; ALT/SGOT, alanine transaminase; AST, aspartate aminotransferase; BPM, breaths per min; CPK, creatine phosphokinase; CRP, C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase, rRT-PCR, real-time reverse transcription polymerase chain reaction; SpO_2, oxygen saturation; WHO-CPS World Health Organization 10-point Clinical Progression Scale.

[a] Body mass index, calculated as weight in kilograms divided by height in meters squared

Discussion

In this trial embedded in the CORIMUNO-19 cohort, we have tested the role of TCZ given to patients with COVID-19 and moderate-to-severe pneumonia who were neither admitted to an ICU nor required high-flow, NIV, or MV. There were no significant differences between those who received TCZ and those who did not on WHO-CPS scores greater than 5 at day 4. The proportion of patients with NIV, HFO, MV or death at day 14 was reduced with TCZ. The probability that TCZ reduced the risk of with NIV, HFO, MV, or death at day 14 was 95%, and the probability that this risk reduction would be higher than 15% (HR<0.85), indicating moderate or greater benefit, was 87%. However, the posterior median HR was 0.58 with 90% CrI of 0.33-1.00. We did not observe any effect on mortality at day 28. According to the protocol, patients were followed until day 90, and long-term results will be reported separately. Even if TCZ had no impact at

Figure 2. Occurrence of Primary Outcome Events During Follow-up



Parameter	Value
Median HR	0.58
90% CrI	0.33-1.00
95% CrI	0.30-1.11
P (HR <1)	0.95
P (HR <0.95)	0.93
P (HR <0.85)	0.87
P (HR <0.8)	0.83

Parameter	Value
Median HR	0.58
90% CrI	0.30-1.09
95% CrI	0.26-1.23
P (HR <1)	0.925
P (HR <0.95)	0.903
P (HR <0.85)	0.844
P (HR <0.8)	0.804

Kaplan-Meier cumulative estimates of probability of (A) the primary outcome, death or ventilation support (mechanical ventilation, high-flow or noninvasive ventilation); B, death or mechanical ventilation; (C) overall survival in the tocilizumab arm compared with the usual care arm. In panel A, events occurring on day 1 occurred on the same day as but after randomization. For the primary event and death or mechanical ventilation, data are analyzed in a bayesian framework, and median posterior HR and 90% credible intervals (CrIs) are presented, together with posterior probabilities of achieving specified effects, in the tables on the right. Overall survival was analyzed in a frequentist framework, so these probabilities were not relevant. HFO indicates high-flow oxygen; MV, mechanical ventilation; NIV, noninvasive ventilation.

day 28 on mortality, it may have an interest both at the individual level by reducing the need for intensive care, which is known to increase the risk of long-term complications, eventually death, and decrease health-related quality of life. In addition, at the collective level, TCZ use may limit the burden on ICUs, an important issue because a shortage of ICU beds was observed in several geographical areas at the peak of the pandemic.

Some observational studies have suggested a possible efficacy of TCZ for patients with moderate, severe, or critical SARS-CoV2 infection in China[16] and France.[17] In a larger retrospective study from Italy, TCZ treatment was associated with a 39% reduction in the need for invasive MV or death, despite an increased frequency of new severe infections (13% vs 4%).[18] The overall safety of TCZ was good in our study, with no increase in adverse or serious adverse events. The TCZ group showed a surprisingly lower rate of serious infections despite decreased neutrophil count and increased rate of neutropenia. These results might be explained by the decreased frequency of transfer to the ICU, and the more frequent use of steroid treatment. Likewise, we found no increase in fre-

Table 2. Number of Patients With Noninvasive Ventilation or High-Flow Oxygen, Mechanical Ventilation, or Death

Variable	Tocilizumab (n = 63)	UC (n = 67)	Difference (95% CI)
Primary outcome by day 14, No.	15	24	
Cumulative incidence, % (95% CI)	24 (13 to 34)	36 (23 to 46)	−12 (−28 to 4)
First event, No.			
NIV/HFO	8	13	
MV	3	8	
Death/DNR order	4	3	
MV or death by day 14, No.			
% (95% CI)	17 (8 to 26)	27 (15 to 37)	−9 (−24 to 5)
First event, No.			
MV	5	14	
Death/DNR order	6	4	
Deaths			
Day 14, No.	7	6	
Survival, % (95% CI)	89 (81 to 97)	91 (84 to 98)	
Day 28, No.	7	8	
Survival, % (95% CI)	89 (81 to 97)	88 (80 to 96)	

Abbreviations: DNR, do not resuscitate; HFO, high-flow oxygen; MV, mechanical ventilation; NIV, noninvasive ventilation.

Table 3. Serious Adverse Events and Causes of Deaths

Adverse events, No. (%)			
Event	Tocilizumab (n = 63)	Usual Care (n = 67)	*P* value
Patients with at least 1 AE	28 (44)	36 (54)	30[a]
Patients with multiple AEs	16 (25)	19 (28)	
No. of events	66	86	.21[b]
Serious adverse events			
Patients with at least 1 SAE	20 (32)	29 (43)	.21[a]
Patients with multiple SAEs	5 (8)	10 (15)	
No. of events	26	57	
Atrial fibrillation	0	1	.003[b]
Anemia	1	4	
Hyperlipasemia	0	1	
Cholestasis	0	2	
Hepatic cytolysis	4	4	
Multiple organ failure (death)	0	1 (1)	
Pulmonary embolism (death)	0	3 (1)	
Fever	2	0	
Hyperkaliemia	0	1	
Hypoglycemia	0	1	
Hypertension	1	0	
Acute renal failure	1	2	
Arterial ischemia	0	2	
Lymphopenia	1	0	
Neutropenia	4	0	
Pneumothorax	0	1	
ARDS (death)	9 (7)	19 (9)[c]	
Bacterial sepsis	2	11	
Fungal sepsis	0	2	
Viral sepsis	0	1	
Tetraparesis	0	1	
Cough	1	0	

Abbreviations: AE, adverse event; ARDS, acute respiratory distress syndrome; SAE, serious adverse event.

[a] Fisher exact test.

[b] Poisson model.

[c] For 1 patient, the cause of death was reported as both ARDS and hemorrhagic shock.

quency of other adverse events such as hepatitis, cardiovascular events or kidney failure.

Strengths of this trial include the multicenter design, a thorough monitoring to ensure data quality and a homogeneous target population of patients with moderate-to-severe pneumonia requiring at least 3 L/min oxygen support. This later point is crucial since drugs like corticosteroids and IL-6 inhibitors might hurt if employed too early, or be ineffective if employed too late. Finding the sweet spot, if one exists, will probably require multiple trials.

In addition, the promising results of DXM in the RECOVERY trial highlight the need to address the relative and combined

effects of TCZ and DXM. Finding the optimal timing and combination, if one exists, will probably require multiple trials.

Limitations

At the beginning of the first COVID-19 pandemic wave, the CORIMUNO-19 cohort was designed to allow for performing quickly several exploratory clinical trials to test some of the many drug candidates of potential interest. Setting up such trials necessitated an adaptation to the crisis context while preserving the major ethical and methodological principles.[20,21] Consequently, this trial has a number of limitations. The trial was not blinded because it was logistically impossible at the time of the pandemic to set up a double-blind study quickly. This probably explains why all the academic-sponsored randomized clinical trials published until now in COVID-19 infection were open randomized clinical trials. Unblinding could lead to measurement bias. However, it is unlikely that investigators knowing which patients have been allocated to a particular therapy would have based their subsequent therapeutic decisions (eg, use MV, HFO, NIV, or turn around ventilation) on such knowledge. Moreover, in most cases, the clinician taking the decision of ventilation assistance was from another department than the ward clinician having included the patient. Furthermore, even using a placebo, the credibility of blinding caregivers could have been debated in some cases given the early evident effect of TCZ on C-reactive protein levels for most patients. Lack of blinding may also lead to performance bias and patients assigned to the UC group received corticosteroids—and especially DXM—twice as often as those in the TCZ group. However, if any related bias exists, it would probably favor the UC arm rather than TCZ because DXM improved outcomes of similar patients in the RECOVERY trial. Another limitation is that UC could differ among centers and over time. However, the short period of accrual and the stratification of randomization may have limited the effect of such lack of standardization. The sample size was small, credibility intervals were wide, and the treatment effect may be overestimated.[22] Also, this study did not allow evaluation of what would be the effect of TCZ used earlier in the disease course. Lastly, we targeted in this trial a narrow segment of the COVID-19 patient population (patients with a WHO-CPS score of 5 exactly and requiring at least 3 L/min oxygen), and these results are not generalizable to other populations.

Conclusions

In this randomized clinical trial of patients with COVID-19 and pneumonia requiring oxygen support but not admitted to the intensive care unit, TCZ did not reduce WHO-CPS scores less than 5 at day 4 but might have reduced the risk of NIV, MV, or death by day 14. No difference on day 28 mortality was found. These findings should be confirmed with a larger randomized clinical trial with longer follow-up. Future studies are needed to help determine which group of patients derive the greatest benefit from the drug and whether combined therapy with corticosteroids or antiviral agents may further improve outcomes.

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Author Contributions: Drs Resche-Rigon and Porcher had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors contributed equally to this study.
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