FAST TRACK

Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial

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ABSTRACT

OBJECTIVE

To determine whether tocilizumab improves clinical outcomes for patients with severe or critical coronavirus disease 2019 (covid-19).

DESIGN

Randomised, open label trial.

SETTING

Nine hospitals in Brazil, 8 May to 17 July 2020.

PARTICIPANTS

Adults with confirmed covid-19 who were receiving supplemental oxygen or mechanical ventilation and had abnormal levels of at least two serum biomarkers (C reactive protein, D dimer, lactate dehydrogenase, or ferritin). The data monitoring committee recommended stopping the trial early, after 129 patients had been enrolled, because of an increased number of deaths at 15 days in the tocilizumab group.

INTERVENTIONS

Tocilizumab (single intravenous infusion of 8 mg/kg) plus standard care (n=65) versus standard care alone (n=64).

MAIN OUTCOME MEASURE

The primary outcome, clinical status measured at 15 days using a seven level ordinal scale, was analysed as a composite of death or mechanical ventilation because the assumption of odds proportionality was not met.

RESULTS

A total of 129 patients were enrolled (mean age 57 (SD 14) years; 68% men) and all completed follow-up. All patients in the tocilizumab group and two in the standard care group received tocilizumab. 18 of 65 (28%) patients in the tocilizumab group and 13 of 64 (20%) in the standard care group were receiving mechanical ventilation or died at day 15 (odds ratio 1.54, 95% confidence interval 0.66 to 3.66; P=0.32). Death at 15 days occurred in 11 (17%) patients in the tocilizumab group compared with 2 (3%) in the standard care group (odds ratio 6.42, 95% confidence interval 1.59 to 43.2). Adverse events were reported in 29 of 67 (43%) patients who received tocilizumab and 21 of 62 (34%) who did not receive tocilizumab.

CONCLUSIONS

In patients with severe or critical covid-19, tocilizumab plus standard care was not superior to standard care alone in improving clinical outcomes at 15 days, and it might increase mortality.

TRIAL REGISTRATION

ClinicalTrials.gov NCT04403685.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In coronavirus disease 2019 (covid-19), an increased level of interleukin 6 correlates with disease severity and mortality

The interleukin 6 inhibitor tocilizumab might mitigate the inflammatory response and improve clinical outcomes of patients with severe or critical covid-19

The effects on clinical outcomes are, however, not well defined

WHAT THIS STUDY ADDS

Among patients with severe or critical covid-19, tocilizumab plus standard care was not superior to standard care alone in improving clinical status at 15 days, and it might increase mortality

Introduction

The coronavirus disease 2019 (covid-19) pandemic has led to profound worldwide health, economic, and social losses.[1-3] As of October 2020, more than 40 million people have received a diagnosis of covid-19 and one million deaths have occurred globally.[1] Although the disease is asymptomatic or mild in most patients, a substantial percentage of people have more extensive pneumonia that can progress to hypoxaemic respiratory failure, shock, dysfunction of organs, and death.[4] Activation of macrophages as a result of infection, initially in the lungs and then systemically, is an essential source of pro-inflammatory cytokines and chemokines.[5 6] This host immune response is thought to play a key role in the pathophysiology of lung and other organ dysfunction in covid-19.[7 8]

Tocilizumab is an interleukin 6 inhibitor approved for the treatment of rheumatoid arthritis, giant cell arteritis, and cytokine release syndrome during

chimeric antigen receptor T cell therapy (CAR-T).[9] Interleukin 6 is an inflammatory cytokine that exerts its effects in the liver and on lymphocytes, inducing acute phase reactants such as C reactive protein, fibrinogen, and hepcidin from hepatocytes, and promotes CD4 T helper 17 and CD8 cytotoxic T cell differentiation and antibody production.[10] Interleukin 6 plays an important role in controlling viral infections such as influenza A, severe acute respiratory syndrome coronavirus 1, and herpesvirus.[11] In covid-19, an increased level of interleukin 6 and C reactive protein correlates with disease severity and mortality.[12 13] Thus, blocking interleukin 6 activity might play a role in mitigating the inflammatory response and improve clinical outcomes in patients with covid-19. To test this hypothesis, we conducted a randomised controlled trial comparing tocilizumab plus standard care with standard care alone in patients admitted to hospital with severe or critical covid-19.

Methods

This multicentre, randomised, open label, parallel group, superiority trial was conducted in nine hospitals across Brazil. The trial protocol and statistical analysis plan were submitted for publication before interim analysis (see supplementary file).[14] Written or electronic consent was obtained from all patients or legal representatives before study enrolment. The trial was overseen by an independent data monitoring committee. Because of an administrative error by the research team, the trial was registered at ClinicalTrials.gov a few days after enrolment of the first patients (see supplementary file). An independent adjudication committee analysed secondary infections and deaths. Details of the trial rationale and methods have been described elsewhere and are provided in the study protocol.[14]

Patients

We enrolled hospital in-patients aged 18 years or older with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, confirmed by reverse transcription-polymerase chain reaction, and with symptoms for more than three days. Eligible patients had severe or critical covid-19,[15] with evidence of pulmonary infiltrates confirmed by chest computed tomography or radiography, and were receiving supplemental oxygen to maintain oxygen saturation greater than 93% or had been receiving mechanical ventilation for less than 24 hours before analysis. In addition, at least two of the following criteria had to be met: D dimer >2.74 nmol/L (>1000 ng/mL), C reactive protein >50 mg/L (>5 mg/dL), ferritin >300 µg/L, or lactate dehydrogenase greater than the upper limit of normal. Exclusion criteria included active uncontrolled infection, raised aspartate aminotransferase or alanine aminotransferase levels greater than five times the upper limit of normal, and renal disease with an estimated glomerular filtration of <30 mL/min/1.72 m^2. See the supplementary file for full details of the inclusion and exclusion criteria.

Trial procedures

Patients were randomised in a 1:1 ratio to receive either standard care or tocilizumab plus standard care, with random blocks of sizes 2, 4, 6, and 8, and stratified by age (<60 and ≥60 years) and sex, according to a computer generated schedule using the sample function of software R 3.6.3 (R Foundation). Allocation concealment was ensured by a central automated web accessed system (REDCap), developed by CZO. The concomitant use of hydroxychloroquine, azithromycin, corticosteroids, and antibiotics was allowed according to standard care per local institutional guidelines for patients with covid-19. Remdesivir was not available in Brazil. In the experimental group, tocilizumab was administered as a single intravenous infusion at a dose of 8 mg/kg (maximum 800 mg).

Data were collected daily, from randomisation until day 29, in the electronic case report forms. Hospital researchers, unblinded to treatment assignment, collected outcome data during the patients' hospital stay. For patients who were discharged before day 15, an interviewer who was unaware of the assigned trial group conducted a structured telephone call with the patient or patient's proxy on or after day 15 to assess vital status and return to routine activities.

Outcomes

The primary outcome was clinical status at 15 days evaluated with the use of a seven level ordinal scale, defined as: level 1—not admitted to hospital and with no limitation in activities, level 2—not admitted to hospital but with limitation in activities, level 3—admitted to hospital and not receiving supplemental oxygen, level 4—admitted to hospital and receiving supplemental oxygen, level 5—admitted to hospital and receiving non-invasive positive pressure ventilation or high flow oxygen through a nasal cannula, level 6—admitted to hospital and receiving mechanical ventilation, and level 7—death.

Secondary outcomes were all cause mortality, ascertained from data analysed to day 28; in-hospital mortality; sequential organ failure assessment score at eight and 15 days; clinical status at eight days, assessed using a six level ordinal scale (see supplementary file), and at 29 days, assessed using a seven level ordinal scale; ventilator-free days within 29 days; time to independence from supplemental oxygen within 29 days; duration of hospital stay; secondary infections; occurrence of thromboembolic events; and adverse events. Other prespecified exploratory outcomes were levels of serum inflammatory markers and cytokines, measured at days 5 and 8 (see supplementary file).

Statistical analysis

We estimated that an initial sample size of 150 patients would provide 80% power to detect an odds ratio of 0.44 of having a higher seven level ordinal scale at 15 days, with a two sided significance level of 5%. The primary analysis followed the intention-to-treat principle, except for adverse events, which were analysed in a safety population that included patients according to

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the drug received, regardless of assigned group. The primary outcome was initially planned to be assessed with ordinal logistic regression assuming proportional odds ratios adjusted for stratification variables (age and sex). Because the assumption of odds proportionality was not met (Brant test P=0.04), we collapsed the seven level ordinal scale into a binary outcome (levels 1 to 5 (alive and not receiving mechanical ventilation) versus levels 6 and 7 (receiving mechanical ventilation or death)) and used logistic regression for assessment, as specified in the statistical analysis plan. The effect on the primary outcome represents the odds ratio for receiving mechanical ventilation or death (levels 6 and 7) versus better clinical levels at day 15.

A sensitivity analysis of the treatment effect on the primary outcome was performed using a per protocol population and considering only patients who received the treatment as assigned. We further conducted a post hoc sensitivity analysis of the effect on the primary outcome adjusting for baseline clinical status on the seven level ordinal scale, owing to imbalance in the baseline distribution of this variable between treatment groups, plus age and sex. Analyses for prespecified subgroups were conducted with interaction terms (see supplementary file).

Secondary outcomes were evaluated by generalised linear regression using appropriate distributions. To account for the competing risks of death we performed a post hoc analysis assessing the treatment effect on duration of hospital admission including only patients who were discharged alive. All models were adjusted for age, as a continuous variable, and sex. Results are presented with corresponding 95% confidence intervals. One interim analysis was planned when 75 patients had completed 15 days of follow-up. An independent data monitoring committee performed the interim analysis.

Analysis was performed with R software (R Core Team).[16] P values are not reported for secondary or exploratory outcomes. The widths of the confidence intervals for secondary and exploratory outcomes were not adjusted for multiple comparisons, thus the intervals should not be used to infer definitive treatment effects.

Patient and public involvement

No patients were involved in setting the research question, or in developing plans for recruitment, design, implementation, and dissemination of the results of this study. The study was conceived under the covid-19 pandemic.

Results

A total of 129 patients were recruited between 8 May and 17 July 2020. The trial was prematurely interrupted on 17 July 2020, after the first interim analysis, in accordance with the recommendation of the data monitoring committee, owing to an excess number of deaths at 15 days in the tocilizumab group (see supplementary file). Because of the rapid rate of enrolment, when complete data for 15 day follow-up was available for the first 75 patients and the first interim analysis was conducted, 129 patients had been enrolled in the trial (first patient enrolled on 8 May 2020). Follow-up for the last patient was completed on 11 August 2020. Table 1 in the supplementary file presents the number of patients enrolled according to site. Sixty five patients were assigned to receive tocilizumab plus standard care, and all were treated accordingly (fig 1). Sixty four patients were assigned to receive standard care alone; however, two patients received tocilizumab at the discretion of the treating doctors. The 15 day follow-up was completed for all patients.

Table 1 and supplementary table S2 present the baseline characteristics of the included patients. Mean age was 57 (SD 14) years and 68% of patients were men (table 1). Hypertension, diabetes, and obesity were the most common comorbidities. Seven per cent of patients were receiving corticosteroids at enrolment. The use of other drugs (antibiotics, antivirals, and corticosteroids) did not differ between the groups in the first 15 days (supplementary table S3). More patients in the tocilizumab group were using supplementary oxygen at enrolment (60% *v* 44%), whereas use of non-invasive ventilation or high flow oxygen through a nasal cannula was higher in the control group (23% *v* 41%).

Primary outcome

Table 2 and supplementary figure S1 show the distribution of the primary outcome (seven level ordinal scale at 15 days) and figure 2 shows patient status over time according to study group. Supplementary table S4 presents the cumulative proportions of the categories on the seven level ordinal scale and shows that the odds proportionality assumption did not hold. The use of tocilizumab was not associated with an improvement in mechanical ventilation or death at 15 days (18 of 65 (28%) patients in the tocilizumab group and 13 of 64 (20%) in the standard care group: odds ratio 1.54, 95% confidence interval 0.66 to 3.66; P=0.32). Death at 15 days, a component of the primary outcome, occurred in 11 (17%) patients in the tocilizumab plus standard care group compared with two (3%) in the standard care group (odds ratio 6.42, 1.59 to 43.2). A prespecified per protocol sensitivity analysis and a post hoc sensitivity analysis adjusted for baseline clinical status on the seven level ordinal scale were also not indicative of treatment benefit (see supplementary file). The effects on the primary outcome were in general similar across prespecified subgroups (supplementary table S6).

Secondary outcomes

Tocilizumab was not associated with either detectable significant differences on mortality up to 28 days (odds ratio 2.70, 95% confidence interval 0.97 to 8.35) or in-hospital mortality (2.70, 0.97 to 8.35) (table 2). Supplementary tables S7 and S8 show the causes of death. Clinical status at day 8 and day 29 was not significantly different between treatment groups.

Table 1 | Baseline characteristics of patients with severe or critical coronavirus disease 2019 and assigned to tocilizumab plus standard care or standard care alone. Values are numbers (percentages) unless stated otherwise

Characteristics	Tocilizumab group (n=65)	Control group (n=64)
Mean (SD) age (years)	57.4 (15.7)	57.5 (13.5)
Men	44 (68)	44 (69)
Mean (SD) days from symptom onset to randomisation	10.0 (3.1)	9.5 (3.0)
Comorbidities:		
Hypertension	30 (46)	34 (53)
Diabetes	22 (34)	20 (31)
Obesity	15 (23)	16 (25)
Heart failure	4 (6)	3 (5)
Myocardial infarction	4 (6)	3 (5)
Chronic obstructive pulmonary disease	2 (3)	2 (3)
Asthma	4 (6)	1 (2)
Chronic kidney disease	5 (8)	1 (2)
Solid malignancy	4 (6)	5 (8)
Haematological malignancy	1 (1)	0 (0)
Previous drug use:		
None	13 (20)	9 (14)
Corticosteroid (>5 mg prednisone for >30 days)	4 (6)	5 (8)
Other immunosuppressants*	5 (5)	2 (3)
Hydroxychloroquine	11 (17)	9 (14)
Azithromycin	23 (35)	31 (48)
Others†	41 (63)	38 (59)
Vasopressor:		
None	56 (86)	57 (89)
Norepinephrine (μg/kg/min):		
≤0.1	5 (8)	5 (8)
>0.1	4 (6)	2 (3)
Clinical status on seven level ordinal scale:		
4: Admitted to hospital, receiving supplemental oxygen	39 (60)	28 (44)
5: Admitted to hospital, receiving non-invasive ventilation or high flow oxygen through nasal cannula	15 (23)	26 (41)
6: Admitted to hospital, receiving mechanical ventilation	11 (17)	10 (16)
Mean (SD) SOFA score	3.4 (1.8)	3.6 (2.1)
Respiratory support by mechanical ventilation	11 (17)	10 (16)
Median (interquartile range) vital signs:		
Respiratory rate (rpm)	20 (18-24)	20 (18-25)
Peripheral oxygen saturation (%)	95 (92-96)	95 (93-96)
Laboratory results:		
Median (interquartile range) PaO_2 (mm Hg)	83 (70-105) (n=54)	85 (68-108) (n=57)
Median (interquartile range) D dimer (nmol/L FEU)	2.7 (1.5-3.6) (n=58)	2.2 (1.6-3.8) (n=61)
Mean (SD) C reactive protein (mg/L)	160 (104) (n=63)	193 (283) (n=63)
Mean (SD) ferritin (μg/L)	1271 (1259) (n=44)	1385 (1031) (n=55)
Mean (SD) LDH (U/L)	588 (243) (n=60)	631 (335) (n=61)
Mean (SD) lactate (mg/dL)	14.9 (6.5) (n=46)	15.0 (7.9) (n=50)
Median (interquartile range) prothrombin time (INR)	1.1 (1.0-1.2) (n=54)	1.1 (1.1-1.2) (n=60)
Median (interquartile range) aPTT	1.0 (0.9-1.1) (n=53)	1.1 (1.0-1.3) (n=59)
Type of in-hospital drugs:		
Heparin	53 (81)	54 (84)
Prophylactic	50/53 (94)	48/54 (89)
Therapeutic	3/53 (6)	6/54 (11)
Corticosteroid:		
None	20 (31)	17 (27)
Prednisone equivalent:		
<0.5 mg/kg/day	14 (21)	13 (20)
≥0.5 and <1.0 mg/kg/day	15 (23)	18 (28)
≥1 mg/kg/day	16 (25)	16 (25)

SOFA=sequential organ failure assessment; PaO_2=partial pressure of oxygen; FEU=fibrinogen equivalent units; LDH=lactate dehydrogenase; INR=international normalised ratio; aPTT=activated partial thrombin.
*Cyclosporin, mycophenolate mofetil, and tacrolimus.
†Antihypertensive (n=33), hypoglycaemic agents (n=22), statins (n=10), thyroid hormones (n=5), anticoagulants (n=4), antidepressants (n=4), anticonvulsants (n=1).

Patients assigned to tocilizumab had a lower duration of hospital stay (mean 11.3 (SD 8.0) *v* 14.7 (8.2) days; rate ratio 0.70, 95% confidence interval 0.55 to 0.87). Duration of hospital stay remained lower in patients assigned to tocilizumab in a post hoc analysis including only patients discharged alive (11.9 (8.4) *v*14.8 (8.6) days; rate ratio 0.75, 0.58 to 0.94). No significant differences were found in other secondary outcomes, including ventilator-free days within 29 days, time to independence from supplemental oxygen within

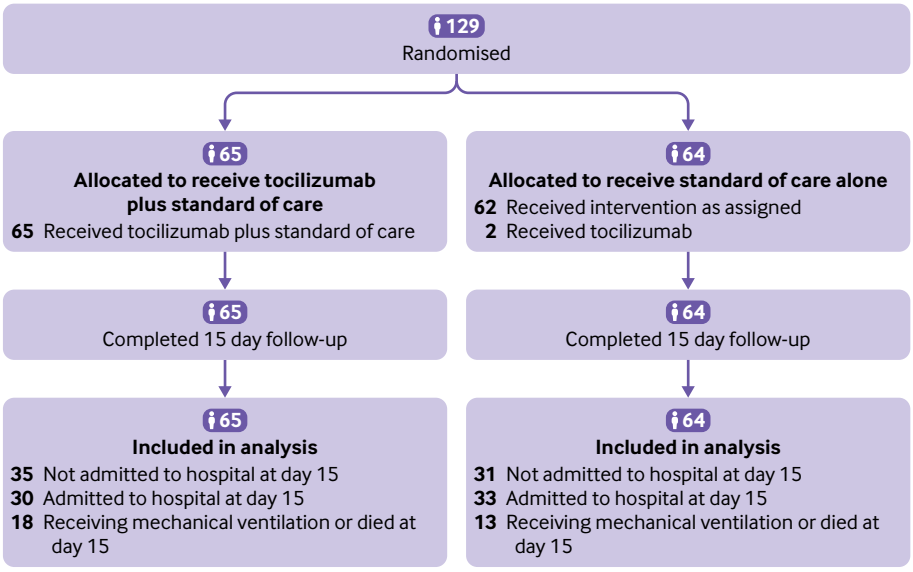

Fig 1 | Allocation, follow-up, and analysis of trial participants

29 days, secondary infections, and thromboembolic events.

Safety

A total of 29 (43%) patients assigned to tocilizumab and 21 (34%) assigned to standard care had adverse events (P=0.26) (table 3). Serious adverse events occurred in 11 (16%) patients in the tocilizumab group and seven (11%) in the standard care alone group. No detectable differences were found in the incidence of any specific adverse event between patients who received tocilizumab compared with those who did not.

Inflammatory markers and cytokines

Levels of interleukin 6 were higher among patients assigned to tocilizumab plus standard care compared with those assigned to standard care alone on days 5 and 8 (see supplementary figure S2 and table S9). Levels of γ interferon were higher on day 5, but not on day 8, among patients assigned to tocilizumab. Among patients assigned to tocilizumab, interleukin 10 was not significantly different on day 5 but was higher on day 8. C reactive protein was lower in the tocilizumab group compared with control group on both day 5 and day 8. No significant difference was found between treatment groups in the serum concentration of other cytokines.

Discussion

In this open label, multicentre, randomised, controlled trial including relatively young (mean age 57 years) patients admitted to hospital with confirmed severe or critical covid-19, the use of the interleukin 6 inhibitor tocilizumab did not result in better clinical outcomes as assessed by a seven level ordinal scale at 15 days. Mortality at 15 days was increased in the group assigned to tocilizumab. Although mortality at 15 days was not a prespecified outcome in the trial, but rather a component of the primary outcome, a detrimental effect on this end point raised concerns about safety, and the data monitoring committee therefore recommended early termination of the trial. Conversely, in both groups, deaths were attributed to covid-19 related acute respiratory failure or multiple organ dysfunction. In addition, at 29 days the effect of tocilizumab on mortality was no longer statistically significant.

Our results were unexpected given the potent anti-inflammatory activity of tocilizumab in rheumatoid arthritis and CAR-T. The rapid increase in cytokines usually accompanies an increase in inflammatory markers and clinical deterioration in patients with covid-19, which is reminiscent of CAR-T.[6 17-19] Thus, it was plausible that blocking interleukin 6 in patients with covid-19 could lessen the inflammatory response and avert some of the more dire consequences of the disease. However, clinical observation and biological plausibility are often not confirmed by randomised clinical trials.[20-23]

The decrease in C reactive protein levels after tocilizumab had been administered suggests an anti-inflammatory effect. Conversely, the increase in serum interleukin 6 levels observed in our study has been described in rheumatoid arthritis and Castleman disease after tocilizumab use.[19] Tocilizumab is a humanised antibody that binds the interleukin 6 receptor inhibiting interleukin 6 signalling. In rheumatoid arthritis, despite an increase in interleukin 6 levels, inflammatory markers and clinical manifestations improve. Thus, the increase in serum interleukin 6 might represent an inhibition of interleukin 6 receptor mediated clearance and continued disease activity.[24] The lack of statistically significant changes in serum interleukin 2, interleukin 4, and tumour necrosis factor-α levels in patients receiving tocilizumab possibly indicates that this treatment intervention did not interfere with the

Table 2 | Primary and secondary outcomes. Values are numbers (percentages) unless stated otherwise

Outcomes	Tocilizumab group (n=65)	Control group (n=64)	Effect estimate	Effect size (95% CI)	P value
Primary endpoint					
Receiving mechanical ventilation or died at day 15*	18 (28)	13 (20)	Odds ratio 1-5 *v* 6-7	1.54 (0.66 to 3.66)	0.32
Clinical status (7 level ordinal scale) at day 15:					
1: Not admitted to hospital, no limitation on activities	32 (49)	26 (41)			
2: Not admitted to hospital, limitation on activities	3 (5)	5 (8)			
3: Admitted to hospital, not receiving supplemental oxygen	6 (9)	6 (9)			
4. Admitted to hospital, receiving supplemental oxygen	6 (9)	10 (16)			
5. Admitted to hospital, receiving non-invasive ventilation or high flow oxygen through nasal cannula	0 (0)	4 (6)			
6: Admitted to hospital, receiving mechanical ventilation	7 (11)	11 (17)			
7: Death	11 (17)	2 (3)			
Secondary endpoints					
Mortality up to 28 days	14 (21)	6 (9)	Odds ratio	2.70 (0.97 to 8.35)	0.07
In-hospital mortality	14 (21)	6 (9)	Odds ratio	2.70 (0.97 to 8.35)	0.02
Mean (SD) SOFA score:					
Day 8	4.1 (3.9)	3.4 (3.0)	Mean ratio	1.20 (0.87 to 1.64)	0.26
Day 15	4.3 (3.6)	4.3 (3.6)	Mean ratio	0.99 (0.65 to 1.49)	0.95
Clinical status (6 level ordinal scale) at day 8:			Odds ratio 1-4 *v* 5-6	0.91 (0.44 to 1.89)	0.79
1: Not admitted to hospital	23 (35)	16 (25)			
2: Admitted to hospital, not receiving supplemental oxygen	7 (11)	7 (11)			
3: Admitted to hospital, receiving supplemental oxygen	10 (15)	12 (19)			
4: Admitted to hospital, receiving non-invasive ventilation or high flow oxygen through nasal cannula	1 (1)	4 (6)			
5: Admitted to hospital, receiving mechanical ventilation	19 (29)	24 (37)			
6: Death	5 (8)	1 (2)			
Clinical status (7 level ordinal scale) at day 29:			Odds ratio 1-5 *v* 6-7	2.17 (0.88 to 5.60)	0.10
1: Not admitted to hospital, no limitation on activities	34 (52)	32 (50)			
2: Not admitted to hospital, limitation on activities	8 (12)	16 (25)			
3: Admitted to hospital, not receiving supplemental oxygen	4 (6)	2 (3)			
4: Admitted to hospital, receiving supplemental oxygen	1 (1)	4 (6)			
5: Admitted to hospital, receiving non-invasive ventilation or high flow nasal cannula	0 (0)	0 (0)			
6: Admitted to hospital, receiving mechanical ventilation	4 (6)	4 (6)			
7: Death†	14 (21)	6 (9)			
Mean (SD) ventilator-free days within 29 days‡	19.4 (12.0)	20.5 (10.8)	Rate ratio	1.12 (0.86 to 1.99)	0.53
Median (interquartile range) time to supplemental oxygen independence within 29 days	6 (5-12)	10 (8-14)	Hazard ratio	1.37 (0.92 to 2.04)	0.12
Mean (SD) duration of hospital stay (days)	11.3 (8.0)	14.7 (8.2)	Rate ratio	0.70 (0.55 to 0.87)	0.001
Secondary infections§	10 (15)	10 (16)	Odds ratio	0.99 (0.37 to 2.67)	0.98
Thromboembolic events¶	3 (5)	4 (6)	Odds ratio	0.72 (0.14 to 3.40)	0.67

SOFA=sequential organ failure assessment.
*Primary outcome, clinical status measured at 15 days using seven level ordinal scale, was analysed as a composite of death or mechanical ventilation as prespecified in the statistical analysis plan because the assumption of proportional odds, necessary to analyse the original seven level ordinal scale, did not hold. P=0.32 for primary outcome analysis.
†Death before day 29; ventilator-free days considered 0.
‡19 deaths were associated with covid-19 related acute respiratory failure or multiple organ dysfunction and one death with covid-19 related cerebral haemorrhage.
§Tocilizumab group: bloodstream (n=5), respiratory (n=5), skin soft issue (n=1). One patient had a respiratory and bloodstream infection. Control group: bloodstream (n=3), respiratory (n=7), indeterminate (n=1), bacteraemia (n=1). One patient had a respiratory infection and bacteraemia.
¶Thromboembolic events included stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolism. Tocilizumab group: deep venous thrombosis (n=2) and stroke (n=1). Control group: pulmonary embolism (n=3) and stroke (n=1).

core events in SARS-CoV-2 infection, but rather is restricted to the modulation of downstream effects of interleukin 6.[24]

These results raise questions about an anti-inflammatory approach in the treatment of covid-19 beyond corticosteroids, which might also have an immune modulation role in covid-19. Dexamethasone was found to be associated with a reduction in 28 day mortality in patients with covid-19 who needed supplemental oxygen or mechanical ventilation.[25] No other anti-inflammatory agents have been shown to be beneficial in covid-19. A single anticytokine approach might not inhibit the breadth of the inflammatory response in covid-19 and could have a limited role as a single agent.

Comparison with other studies

Non-randomised studies have suggested that tocilizumab might have a role in controlling cytokine release syndrome associated with covid-19.[26-34] Most observational studies, although not all, suggest a benefit of tocilizumab on clinical outcomes.[26 30 31 33] Results from observational studies are, however, limited owing to a high risk of confounding. Conversely, randomised controlled trials have not shown a beneficial effect of tocilizumab on their respective

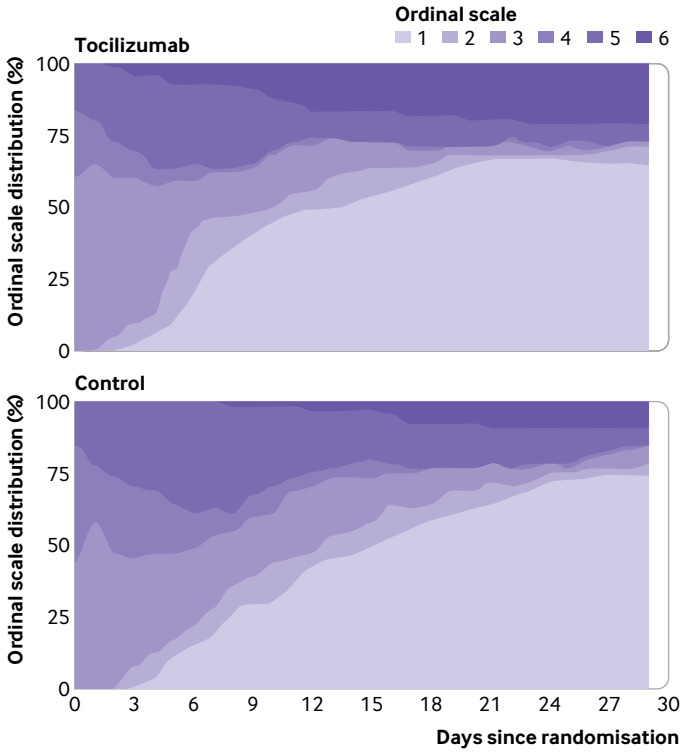

Fig 2 | Relative distribution of patient status over time stratified by treatment group. Six level ordinal scale—1: not admitted to hospital; 2: admitted to hospital, not receiving supplemental oxygen; 3: admitted to hospital, receiving supplemental oxygen; 4: admitted to hospital, receiving non-invasive ventilation or high flow oxygen through a nasal cannula; 5: receiving mechanical ventilation; 6: death

primary outcomes.[20-23] In the Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA), enrolling 452 hypoxaemic patients, tocilizumab had no effect on clinical outcomes at 28 days, assessed with the seven level ordinal scale.[20] Length of intensive care unit and hospital stay, however, were lower among patients assigned to tocilizumab. The CORIMUNO trial included 131 hypoxaemic patients and did not show an effect of tocilizumab on clinical outcomes at 28 days.[21] The Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial randomised 242 hypoxaemic patients and reported no difference in time to intubation or death during 28 days.[22] Another study, which enrolled 126 hypoxaemic patients, reported no benefit on disease progression at day 14.[23]

Identifying a population that would likely benefit from tocilizumab has not been possible so far. We found no benefit of tocilizumab among patients with a more pronounced inflammatory phenotype and concurrent lung damage, defined by an increase of at least two laboratory markers and hypoxaemia. Observational studies have suggested that a beneficial effect of tocilizumab is related to starting treatment early in the course of illness.[35-38] For example, in the STOP-covid trial[35] tocilizumab was associated with decreased mortality only among patients with a time from onset of symptoms to intensive care unit admission equal to or lower than three days. Conversely, in all randomised trials assessing tocilizumab, including our trial, average duration of symptoms at baseline ranged from 8 to 12 days.[20-23] Nevertheless, in a post hoc subgroup analysis, we found no evidence that earlier (≤10 days) versus later (>10 days) initiation of tocilizumab modifies the treatment effect of tocilizumab on clinical outcomes (see supplementary table S10).

Limitations of this study

Our baseline data were well balanced, except for respiratory support and use of azithromycin. The level of respiratory support, an important prognostic marker, was lower among patients assigned to tocilizumab.

Table 3 | Adverse events (safety population). Values are numbers (percentages)

Events	Tocilizumab group (n=67)	Control group (n=62)	P value
Any adverse events	29 (43)	21 (34)	0.26
Reported severe adverse event, according to classification*:			
Any severe adverse event	11 (16)	7 (11)	0.45
Raised ALT, AST, or bilirubin level	7 (10)	3 (5)	0.33
Anaemia	3 (4)	3 (5)	1.00
Pneumothorax	0 (0)	1 (2)	0.48
Neutropenia	1 (1)	0 (0)	1.00
Bleeding	1 (1)	0 (0)	1.00
Intracranial bleeding	0 (0)	1 (2)	1.00
Sudden cardiorespiratory collapse	4 (6)	1 (2)	0.37
Non-severe adverse events:			
Any non-severe adverse event	24 (36)	15 (24)	0.18
Raised ALT, AST, or bilirubin level	11 (16)	4 (6)	0.10
Anaemia	7 (10)	10 (16)	0.44
Haemorrhage	1 (1)	1 (2)	1.00
Neutropenia	1 (1)	0 (0)	1.00
Thrombocytopenia	4 (6)	0 (0)	0.12
Neutrophilia	1 (1)	0 (0)	1.00
Anxiety	1 (1)	0 (0)	1.00
Lymphopenia	0 (0.0)	1 (2)	1.00
Atrial fibrillation	1 (1)	0 (0)	1.00
Hypoacusis	1 (1)	0 (0)	1.00

ALT=alanine aminotransferase; AST=aspartate aminotransferase.
*Safety population included patients according to drug received (as treated), regardless of assigned group.

The results of a post hoc analysis adjusted for baseline levels of respiratory support were consistent with those of the main analysis and did not show a significant effect on the primary outcome. Although baseline use of azithromycin was less common among patients assigned to tocilizumab, the drug has proven to be ineffective for patients admitted to hospital with covid-19.[39-41]

Our trial has other limitations. Firstly, it was an open label trial. Although assessment of the primary outcome, a seven level ordinal scale at 15 days, is objective, the decision to perform tracheal intubation and its timing depends on the operator. Secondly, the sample size was relatively small. Thus the 95% confidence interval around the effect on the primary outcome was wide, compatible with odds ratios between 0.66 (benefit of tocilizumab) and 3.66 (harm with tocilizumab). Thirdly, the distribution of the seven level ordinal scale at 15 days was not compatible with proportional odds assumptions, which required reclassification of the outcome as a binary variable. This finding led to a further reduction in the statistical power to detect a treatment effect on the primary outcome. Fourthly, we did not record the number of patients assessed for eligibility. Fifthly, after randomisation we collected information on concomitant treatment into broad classes: antivirals, corticosteroids, and antibiotics. These co-interventions were administered similarly for patients assigned to both treatment groups up to day 15. However, we are unable to report on use of these drugs according to specific agents. In any case, except for corticosteroids, and possibly remdesivir (not available in Brazil), no antiviral or antibiotic has been shown to modify the clinical course of patients admitted to hospital with covid-19.[39-41]

Conclusions

In this trial including patients admitted to hospital with severe or critical covid-19, the use of tocilizumab plus standard care was not superior to standard care alone in improving patients' clinical status at 15 days, and might have increased mortality.

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The collaborators are listed in the supplementary file. The trial was designed by the executive committee (see supplementary file). The executive committee vouches for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Contributors: ABC, DLCF, JP, PS, and VCV conceived the study, wrote the protocol, recruited patients, and drafted the manuscript. ABC, RGR, FRM, FGZ, OB, LCPA, RDL, AA, LKD, and CGC developed the protocol and approved the final version for the Coalition covid-19 Brazil Group, recruited patients, participated in interim discussions, and reviewed the manuscript. CZO developed the REDCap database and attended to all data collection related issues. LPD and LMI performed the statistical analysis. LECA, AFS, and MCP coordinated exploratory sample collection and will be performing the exploratory analysis, participated in the protocol development an interim discussion and reviewed the manuscript. VCV, ABC, DLCF, JP, and PS act as guarantors, accept full responsibility for the work, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: This trial was approved by the Brazilian National Commission for Research Ethics and the ethics committees at all participating sites.

Data sharing: Deidentified participant data and a dictionary of variables will be available to clinical researchers three months after publication on request to the corresponding author at viviane.veiga@bp.org.br. The Coalition covid-19 Brazil executive committee will oversee and decide about the use of the study data upon receiving a reasonable request. The executive committee reviewed and commented on any draft manuscripts before publication.

The lead author (VCV) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: There are no plans to disseminate the results of the research to study participants. Study results will be shared with the public through press release, social media, conference presentations, and https://www.bp.org.br.

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Supplementary information: additional information, tables S1-S10, and figures S1 and S2