Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial

Arvinder S Soin, Kuldeep Kumar, Narendra S Choudhary, Pooja Sharma, Yatin Mehta, Sushila Kataria, Deepak Govil, Vikas Deswal, Dhruva Chaudhry, Pawan Kumar Singh, Ashish Gupta, Vikas Agarwal, Suresh Kumar, Shashikala A Sangle, Rajesh Chawla, Suneetha Narreddy, Rahul Pandit, Vipul Mishra, Manoj Goel, Athimalaipet V Ramanan

Summary

Background Global randomised controlled trials of the anti-IL-6 receptor antibody tocilizumab in patients admitted to hospital with COVID-19 have shown conflicting results but potential decreases in time to discharge and burden on intensive care. Tocilizumab reduced progression to mechanical ventilation and death in a trial population enriched for racial and ethnic minorities. We aimed to investigate whether tocilizumab treatment could prevent COVID-19 progression in the first multicentre randomised controlled trial of tocilizumab done entirely in a lower-middle-income country.

Methods COVINTOC is an open-label, multicentre, randomised, controlled, phase 3 trial done at 12 public and private hospitals across India. Adults (aged ≥18 years) admitted to hospital with moderate to severe COVID-19 (Indian Ministry of Health grading) confirmed by positive SARS-CoV-2 PCR result were randomly assigned (1:1 block randomisation) to receive tocilizumab 6 mg/kg plus standard care (the tocilizumab group) or standard care alone (the standard care group). The primary endpoint was progression of COVID-19 (from moderate to severe or from severe to death) up to day 14 in the modified intention-to-treat population of all participants who had at least one post-baseline assessment for the primary endpoint. Safety was assessed in all randomly assigned patients. The trial is completed and registered with the Clinical Trials Registry India (CTRI/2020/05/025369).

Findings 180 patients were recruited between May 30, 2020, and Aug 31, 2020, and randomly assigned to the tocilizumab group (n=90) or the standard care group (n=90). One patient randomly assigned to the standard care group inadvertently received tocilizumab at baseline and was included in the tocilizumab group for all analyses. One patient randomly assigned to the standard care group withdrew consent after the baseline visit and did not receive any study medication and was not included in the modified intention-to-treat population but was still included in safety analyses. 75 (82%) of 91 in the tocilizumab group and 68 (76%) of 89 in the standard care group completed 28 days of follow-up. Progression of COVID-19 up to day 14 occurred in eight (9%) of 91 patients in the tocilizumab group and 11 (13%) of 88 in the standard care group (difference −3·71 [95% CI −18·23 to 11·19]; p=0·42). 33 (36%) of 91 patients in the tocilizumab group and 22 (25%) of 89 patients in the standard care group had adverse events; 18 (20%) and 15 (17%) had serious adverse events. The most common adverse event was acute respiratory distress syndrome, reported in seven (8%) patients in each group. Grade 3 adverse events were reported in two (2%) patients in the tocilizumab group and five (6%) patients in the standard care group. There were no grade 4 adverse events. Serious adverse events were reported in 18 (20%) patients in the tocilizumab group and 15 (17%) in the standard care group; 13 (14%) and 15 (17%) patients died during the study.

Interpretation Routine use of tocilizumab in patients admitted to hospital with moderate to severe COVID-19 is not supported. However, post-hoc evidence from this study suggests tocilizumab might still be effective in patients with severe COVID-19 and so should be investigated further in future studies.

Funding Medanta Institute of Education and Research, Roche India, Cipla India, and Action COVID-19 India.

Lancet Respir Med 2021; 9: 511–21

Published Online March 4, 2021 https://doi.org/10.1016/S2213-2600(21)00081-3

See Comment page 438

Medanta Institute of Education and Research, Medanta—The Medicity Hospital, Gurugram, Haryana, India (A S Soin MS, K Kumar MSc, N S Choudhary DM, P Sharma MD); **Medanta—The Medicity Hospital, Gurugram, Haryana, India** (Y Mehta MD, S Kataria PGDMLS, D Govil MD, V Deswal MD); **Postgraduate Institute of Medical Sciences, Rohtak, Haryana, India** (Prof D Chaudhry DM, Prof P K Singh DM); **Medeor Hospital, Manesar, Haryana, India** (A Gupta DA); **Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India** (Prof V Agarwal DM); **Apollo Hospitals Chennai, Tamil Nadu, India** (S Kumar MD); **BJ Medical College, Pune, Maharashtra, India** (Prof S A Sangle MD); **Indraprastha Apollo Hospital, New Delhi, India** (R Chawla MD); **Apollo Hospital Hyderabad, Telangana, India** (S Narreddy MD); **Fortis Mulund, Mumbai, Maharashtra, India** (R Pandit MD); **Nayati Hospitals, Agra, Uttar Pradesh, India** (V Mishra MD); **Fortis Memorial Research Institute, Gurugram, Haryana, India** (M Goel MD); **University Hospitals Bristol NHS Foundation Trust and Translational Health Sciences, Bristol Medical School, Bristol, UK** (Prof A V Ramanan FRCP)

Introduction

There is a need for effective treatment options for COVID-19, especially in low-income and middle-income countries (LMICs) with a high disease burden and scarce resources. Dexamethasone has been shown to reduce mortality rates in patients admitted to hospital with COVID-19[1] and some evidence indicates that antiviral therapy with remdesivir might improve disease recovery times in patients with severe COVID-19, but it does not appear to reduce mortality rates.[2]

In SARS-CoV-2 infection, proinflammatory cytokines, including IL-6, can cause hyperinflammation.[3,4] Patients

Correspondence to:
Dr Arvinder S Soin, Medanta Institute of Education and Research, Medanta–The Medicity Hospital, Gurugram, Haryana 122 001, India
avisoin1@gmail.com

Research in context

Evidence before this study

We did a PubMed search of "tocilizumab AND (COVID-19 OR coronavirus)" on April 30, 2020, with no language or publication date restrictions. A total of 75 articles were retrieved, which included 13 case reports or observational studies of patients with COVID-19 treated with tocilizumab. Evidence from case reports and observational cohort studies suggested that patients admitted to hospital with COVID-19 pneumonia and cytokine release syndrome treated with tocilizumab had some clinical benefits, including resolution of fever, reduced need for oxygen supplementation and mechanical ventilation, and shortened hospital stay. No randomised controlled trials (RCTs) of tocilizumab in patients with COVID-19 had been completed at the time this study was initiated.

Added value of this study

To our knowledge, this is the first multicentre randomised controlled phase 3 trial of tocilizumab in patients with COVID-19 in India. The trial was conducted across multiple sites under difficult conditions in a country that has the second highest COVID-19 caseload in the world. This study shows that, similar to results of other RCTs of tocilizumab published after initiation of this trial, tocilizumab is not an effective therapeutic option for adults with COVID-19, although there might be a role for it in adults with severe COVID-19 in India.

Implications of all available evidence

The published RCTs assessing tocilizumab in COVID-19-associated pneumonia have not provided clear evidence either confirming or completely refuting a potential effective role of tocilizumab, although they agree on an acceptable safety profile similar to usual care in this condition. This RCT done in India highlights, as do other studies, that tocilizumab is not an effective routine therapy for COVID-19 in all patients. However, there is a suggestion that some subgroups of patients might benefit from this therapy; this awaits further clarification from additional RCTs that are underway.

with severe and critical disease often progress to respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ failure.[5,6] In COVID-19, the level of IL-6, a proinflammatory cytokine, is increased,[7] correlates with the severity of pneumonia,[8–10] and appears to drive immune dysregulation.[4]

Tocilizumab is an anti-IL-6 receptor-α monoclonal antibody that is indicated for the treatment of some IL-6-mediated inflammatory disorders.[11] Case reports and observational studies suggest that tocilizumab might be a promising treatment option in COVID-19-associated pneumonia,[12–14] supporting further investigation in randomised controlled trials. No randomised controlled trial assessing tocilizumab in patients with COVID-19 had been completed at the time our study was initiated. However, four trials have since reported conflicting and mostly negative results regarding the efficacy of this treatment.[15–18] Guidelines for the conduct of clinical trials during the COVID-19 pandemic have been provided by the Indian Ministry of Health and Family Welfare (MoHFW) based on guidance issued by the US Food and Drug administration.[19] To ensure standardised reporting and comparison of therapeutic options in homogeneous disease populations, the Drug Controller General of India suggested that the MoHFW grading of COVID-19 disease severity[20] be followed in all COVID-19 drug trials in India. This simple grading system, designed for optimal use of scarce health-care resources, is based on oxygen saturation and triaging priorities for patients whereby those with mild disease can be managed at home or at a non-medical facility, those with moderate disease can be treated at a health-care facility but not in an intensive care unit (ICU), and those with severe disease can receive tertiary-level institutional care.

See Online for appendix

The COVID India Tocilizumab (COVINTOC) trial is, to our knowledge, the first randomised controlled trial of tocilizumab in COVID-19 done entirely in an LMIC. Tocilizumab plus standard care was compared with standard care alone to investigate whether tocilizumab treatment could prevent COVID-19 progression in patients admitted to hospital with moderate to severe disease.

Methods

Study design and participants

COVINTOC is an open-label, multicentre, randomised, controlled, phase 3 trial to investigate the clinical outcomes and safety of tocilizumab plus local standard care versus local standard care alone in patients with moderate to severe COVID-19. After approval by the Drug Controller General of India, the study was done at 12 public and private hospitals across India (appendix p 6). Patients aged 18 years or older admitted to hospital with SARS-CoV-2 infection confirmed by WHO criteria (positive PCR test on any specimen) and moderate to severe disease defined according to the Indian MoHFW clinical management protocol for COVID-19[20] (moderate defined as respiratory rate 15–30 per min [revised to 24 per min on June 13, 2020] and blood oxygen saturation [SpO_2] 90–94%; and severe defined as respiratory rate ≥30 per min or SpO_2 <90% in ambient air, or ARDS or septic shock; appendix p 4) were eligible. Patients with known severe allergic reaction to tocilizumab or other monoclonal antibodies; active tuberculosis infection; suspected or active bacterial, fungal, or viral infection (except treated hepatitis C or B), or any other infection except COVID-19 were excluded. Patients were also excluded if the investigator deemed that death was

imminent and inevitable within 24 h. Patients could not have received any oral anti-rejection or immunomodulatory drugs in the previous 6 months or treatment with any investigational agent (including antivirals, cell-depleting therapies, biologics, and Janus kinase inhibitors) within five half-lives or 30 days before randomisation, whichever was longer. Patients were excluded if the investigator judged that they had any serious medical conditions or laboratory abnormalities that precluded safe participation in and completion of the study. Patients could not have a diagnosis of immune-related rheumatic disease or be receiving corticosteroids equivalent to methylprednisolone at a dose of more than 1 mg/kg per day at screening or baseline. Laboratory exclusion criteria were absolute neutrophil count less than 500 cells per µL, platelet count less than 50 000 cells per µL, and alanine aminotransferase or aspartate aminotransferase concentrations more than ten times the upper limit of normal within 24 h of screening or baseline (appendix p 1).

All patients or their legally acceptable representatives provided written informed consent to participate in the study. The study was conducted in accordance with International Conference on Harmonisation–Good Clinical Practice (ICH-GCP) guidelines, the Declaration of Helsinki, and local regulatory requirements. The protocol and any amendments were approved by the institutional review board or ethics committee at each study site in accordance with local regulations and ICH-GCP. The full protocol and details of any changes are in the appendix (p 8).

Randomisation and masking

Eligible patients were randomly assigned using block randomisation in a 1:1 ratio to receive open-label tocilizumab plus current standard care (tocilizumab group) or current standard care alone (standard care group). The randomisation sequence was generated using SAS, version 9.4 and an interactive web response system. Randomisation numbers were assigned in sequential order to the study sites according to the pregenerated sequence provided by the investigational medicinal product team at the Medanta Institute of Education and Research. After randomisation, none of the study personnel or patients were masked to treatment assignment in this open-label trial.

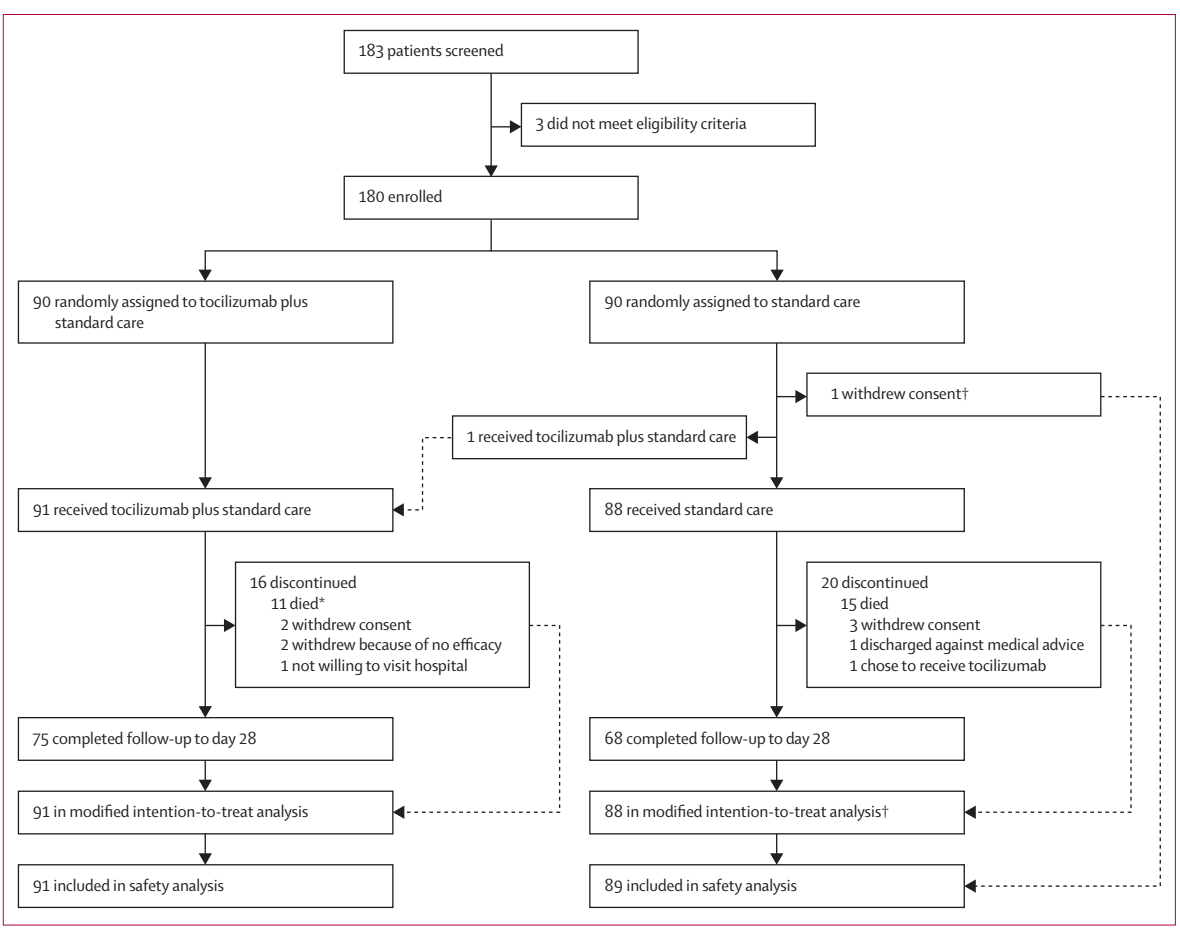

Figure 1: **Patient disposition**

*Two additional deaths were reported after day 28. †One patient randomly assigned to the standard care group withdrew consent after the baseline visit.

	Tocilizumab group (n=91)	Standard care group (n=88)
Sex		
Female	15 (16%)	12 (14%)
Male	76 (84%)	76 (86%)
Age, years		
Median (IQR)	56 (47–63)	54 (43–63)
18–60 years	62 (68%)	58 (66%)
>60 years	29 (32%)	30 (34%)
Body-mass index, kg/m²	27·0 (4·4)	26·8 (4·6)
Comorbidities		
Type 2 diabetes	31 (34%)	43 (49%)
Hypertension	36 (40%)	34 (39%)
Chronic obstructive pulmonary disease	1 (1%)	3 (3%)
Respiratory, thoracic, and mediastinal disorders	4 (4%)	3 (3%)
Renal and urinary disorders	4 (4%)	4 (5%)
Cardiac disorders	15 (16%)	12 (14%)
Laboratory measures		
IL-6, pg/mL	115·5 (245·6)	85·2 (232·2)
C-reactive protein, mg/L	110·7 (107·2)	88·1 (81·1)
Ferritin, ng/mL	920·6 (755·2)	692·7 (501·6)
Disease severity		
Moderate	41 (45%)	47 (53%)
Severe	50 (55%)	41 (47%)
Received other medicines during the study		
All patients		
Remdesivir	39 (43%)	36 (41%)
Corticosteroids	83 (91%)	80 (91%)
Moderate COVID-19		
Remdesivir	18/41 (44%)	21/47 (45%)
Corticosteroids	35/41 (85%)	42/47 (89%)
Severe COVID-19		
Remdesivir	21/50 (42%)	15/41 (37%)
Corticosteroids	48/50 (96%)	38/41 (93%)

(Table 1 continues in next column

(Continued from previous column)

	Tocilizumab group (n=91)	Standard care group (n=88)
Respiratory support		
All patients		
Supplemental oxygen	81 (89%)	80 (91%)
Non-invasive bilevel positive airway pressure ventilation	28 (31%)	20 (23%)
Mechanical ventilation	5 (5%)	4 (5%)
Intensive care unit	64 (70%)	54 (61%)
Moderate COVID-19		
Supplemental oxygen	32/41 (78%)	39/47 (83%)
Non-invasive bilevel positive airway pressure ventilation	5/41 (12%)	6/47 (13%)
Mechanical ventilation	0	0
Intensive care unit	24/41 (59%)	22/47 (47%)
Severe COVID-19		
Supplemental oxygen	49/50 (98%)	41/41 (100%)
Non-invasive bilevel positive airway pressure ventilation	23/50 (46%)	14/41 (34%)
Mechanical ventilation	5/50 (10%)	4/41 (10%)
Intensive care unit	40/50 (80%)	32/41 (78%)

Data are n (%) or mean (SD) unless otherwise stated.

Table 1: **Baseline demographics and clinical characteristics (modified intention-to-treat population)**

Procedures

Tocilizumab was administered as a single intravenous infusion at 6 mg/kg up to a maximum dose of 480 mg. An additional dose of 6 mg/kg (max 480 mg/kg) could be administered if clinical symptoms worsened or did not show improvement within 12 h to 7 days after administration of the first dose. The dosing regimen was selected on the basis of the cost and supply considerations in India and because a single dose between 4 mg/kg and 8 mg/kg plus an additional dose to a maximum of 800 mg, if required, has been recommended on the basis of initial reports on the use of tocilizumab in the treatment of COVID-19 in China.[21] Standard care was provided according to the protocols at the individual study sites. It was recommended that patients undergo routine laboratory testing and undergo chest x-ray or CT and electrocardiography in the 3 days before baseline. Other tests could be done as deemed necessary by the treating physician. Pharmacological treatment was administered on the basis of data available at the time from uncontrolled trials in accordance with policies at the individual hospitals. Corticosteroids equivalent to methylprednisolone at a dose of 1 mg/kg or less were permitted if deemed necessary by the treating physician. Supplemental oxygen was recommended to treat hypoxia, and high-flow nasal cannula, non-invasive ventilation, and mechanical ventilation could be considered if hypoxia and respiratory distress progressed. Treatments for shock or hypovolaemia, symptoms such as fever and myalgia, and comorbid conditions could be administered if deemed necessary by the treating physician. Randomly assigned patients were treated at the baseline visit (study day 0), monitored closely during hospital stay, and followed up for 30 days after randomisation. Scheduled visits were done at the clinic daily until hospital discharge then at day 14 (+2), day 21 (±2), and day 28 (±2), and by telephone on day 18 and day 24. Assessments at scheduled clinic visits included physical examination, vital signs, oxygen saturation, laboratory tests, and adverse events and serious adverse events. At telephone appointments, clinical complaints, adverse events and serious adverse events, clinical status, and concomitant medications were recorded.

Outcomes

The primary efficacy endpoint was the proportion of patients with progression of COVID-19 from moderate to severe or from severe to death up to day 14. Secondary

	Tocilizumab group (n=91)	Standard care group (n=88)	Difference (95% CI)	p value
Primary endpoint				
Patients with progressive COVID-19 up to day 14	8 (9%)	11 (13%)	−3·7 (−18·2 to 11·2)*	0·42†
Secondary endpoints				
Patients with at least a one-grade improvement in cytokine release syndrome up to day 28	58 (64%)	59 (67%)	−3·3 (−17·9 to 11·3)*	0·64†
Incidence of mechanical ventilation up to day 28	14 (15%)	13 (15%)	0·6 (−9·9 to 11·1)	0·91†
Ventilator-free days				
Mean (SD)	24·3 (9·2)	23·2 (10·6)	..	0·45‡
Median (IQR)	28·0 (28·0 to 28·0)	28·0 (28·0 to 28·0)	..	..
Organ failure-free days				
Mean (SD)	24·6 (9·2)	23·2 (10·6)	..	0·35‡
Median (IQR)	28·0 (28·0 to 28·0)	28·0 (28·0 to 28·0)	..	..
Incidence of ICU admission	71 (78%)	64 (73%)	5·3 (−7·3 to 17·9)*	0·41
Duration of ICU stay, days				
Mean (SD)	8·2 (6·2)	8·4 (6·5)	..	0·91
Median (IQR)	7·0 (3·0 to 10·0)	6·0 (3·5 to 11·0)	..	..
Duration of supplemental oxygen-free days				
Mean (SD)	17·1 (9·4)	18·3 (9·9)	..	0·41
Median (IQR)	20·0 (12·0 to 24·0)	22·0 (16·0 to 25·0)	..	..
Mortality				
Day 7	2 (2%)	2 (2%)	−0·1 (−4·4 to 4·3)	0·97§
Day 14	8 (9%)	9 (10%)	−1·4 (−10·0 to 7·2)	0·74§
Day 21	10 (11%)	14 (16%)	−4·9 (−14·9 to 5·1)	0·33§
Day 28	11 (12%)	15 (17%)	−5·0 (−15·3 to 5·4)	0·35§
Patients who required renal replacement therapy	1 (1%)	6 (7%)	−5·7 (−11·4 to −0·0)	0·049§
Patients with adverse events up to day 28	30/91 (33%)	22/89 (25%)	..	NA
Patients with serious adverse events up to day 28	15/91 (16%)	15/89 (17%)	..	NA
Patients with post-treatment infections up to day 28	5/91 (5%)	5/89 (6%)	..	NA
IL-6 change from baseline to day 7, pg/mL				
N	57	57	..	..
Median (IQR)	37·9 (−6·3 to 105·2)	−4·3 (−20·0 to 6·3)	..	0·0013¶
C-reactive protein change from baseline to day 7, mg/L				
N	53	52	..	..
Median (IQR)	−66·7 (−185·0 to −26·5)	−53·0 (−108·7 to −18·5)	..	0·15¶
Ferritin change from baseline to day 7, ng/mL				
N	54	52	..	..
Median (IQR)	−148·5 (−437·0 to −16·5)	−64·0 (−242·3 to 80·6)	..	0·0601¶

Data are n (%) or n/N (%) unless otherwise stated. Progressive COVID-19 is defined as progressing from moderate to severe disease or from severe disease to death. ICU=intensive care unit. NA=not assessed. *Binomial proportion test. †χ^2 test. ‡Two-sample *t* test. §Z test. ¶Mann-Whitney U test for comparing change from baseline between treatment groups.

Table 2: **Efficacy outcomes (modified intention-to-treat population)**

efficacy endpoints were the proportion of patients with improvement of at least one American Society for Transplantation and Cellular Therapy cytokine release syndrome grade,[22] time to clinical improvement (defined as National Early Warning Score 2 [NEWS2] ≤2 maintained for 24 h), ventilator-free days, organ failure-free days, proportion of patients who were admitted to the ICU, ICU-free days, time to clinical improvement according to COVID-19 grade, time to hospital discharge, and time to negative result on RT-PCR, all up to day 28, and mortality up to days 7, 14, 21, and 28. Serum concentrations of IL-6, ferritin, and C-reactive protein (CRP); proportions of patients with adverse events, serious adverse events, and post-treatment infections; and requirement for renal replacement therapy, all up to day 28, were also secondary endpoints. All outcomes are in the appendix (p 3).

For time-to-event endpoints, such as time to clinical improvement (NEWS2 score) and time to improvement with respect to COVID-19 grading, patients who died during the 28-day period without reaching the endpoint were censored at day 28 to indicate that they did not have an improvement by the end of the study. For

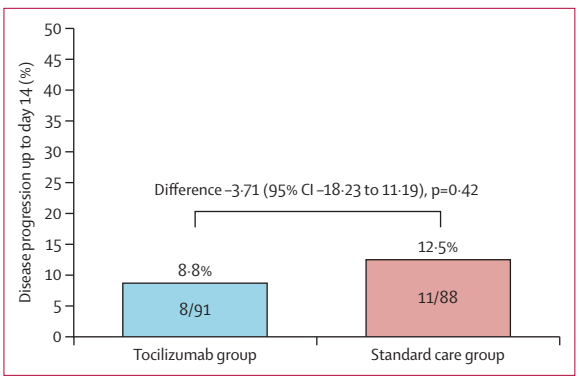

Figure 2: **COVID-19 progression up to day 14 (primary endpoint)**
Proportions of patients with COVID-19 progression up to day 14 (modified intention-to-treat population).

mechanical ventilator-free days and organ failure-free days, zero days was assigned if the patient died within 28 days; otherwise, 28 days minus the number of days on ventilation was assigned as the number of days the patient was on a mechanical ventilator. For ICU stay, the actual duration was presented; for patients who died, the number of days a patient was in ICU was presented.

Safety was monitored by clinical examination, vital signs, laboratory investigations, adverse events, and serious adverse events, as assessed by the investigator during the study. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[23]

Statistical analysis

A sample size of 81 patients in each treatment group was estimated to provide 80% power, with a two-sided 5% type 1 error rate, to establish a difference between the tocilizumab group and the standard care group for the primary endpoint. We assumed progression of clinical severity of COVID-19 from moderate to severe or from severe to death would occur in 20% of patients in the tocilizumab plus standard care group and in 40% of patients in the standard care alone group. Assuming a dropout rate of 10%, we aimed to enrol 90 patients in each treatment group.

Descriptive statistics, including the number of non-missing observations (n), mean (SD), and median (IQR) were established for continuous variables. Minimum and maximum frequency counts and percentages were established for categorical variables. The primary endpoint was reported as the proportion of patients who progressed or died with the 95% CI, and significance tested using a two-proportion Z test or χ^2 test. Differences between treatment groups in the secondary endpoints were assessed using a two-proportion Z test or χ^2 test for categorical variables and a two-sample *t* test or Mann-Whitney U test for continuous variables; paired *t* test was used for change in concentrations of IL-6, ferritin, and CRP. No multiplicity adjustment was planned in this study because only one primary endpoint was to be tested.

Safety was summarised descriptively, and adverse events and serious adverse events were assessed as the frequency and proportion of patients reporting the event and the total count of the number of events. No imputation was performed for missing safety data.

Primary and secondary efficacy analyses were done in the modified intention-to-treat population, which included all randomly assigned patients who had at least one post-baseline assessment for the primary endpoint. Overall safety was assessed in the safety population, which included all randomly assigned patients.

All analyses were performed using SAS, version 9.4. This study is registered with the Clinical Trials Registry India (CTRI/2020/05/025369).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between May 30, 2020, and Aug 31, 2020, 183 patients were screened, of whom 180 met eligibility criteria for enrolment and randomisation (figure 1; appendix p 1). 90 patients were randomly assigned to receive tocilizumab plus standard care (tocilizumab group) and 90 were assigned to receive standard care alone (standard care group). The safety population included 180 patients, and the modified intent-to-treat population included 179 patients because one patient randomly assigned to the standard care group withdrew consent after the baseline visit and did not receive any study medication. Another patient randomly assigned to the standard care group inadvertently received tocilizumab at baseline and was included in the tocilizumab group for all analyses. 143 (79%) of 180 patients completed 28 days of follow-up, 75 (82%) in the tocilizumab group and 68 (76%) in the standard care group. Two patients in the tocilizumab group died after day 28.

Baseline demographics and clinical characteristics were generally balanced between the treatment groups (table 1). Most patients (161 [90%] of 179) were receiving supplemental oxygen, and few (nine [5%]) were on invasive mechanical ventilation at baseline. There was a slightly higher proportion of patients with diabetes in the standard care group (43 [49%] of 88) than in the tocilizumab group (31 [34%] of 91). The proportions of patients with moderate and severe COVID-19 and proportions of patients who received remdesivir or concomitant corticosteroids during the study were similar between the tocilizumab group and the standard care group (table 1).

The proportion of patients with progressive COVID-19 (ie, progression from moderate to severe disease or from severe disease to death) up to day 14 was 9% (eight of 91)

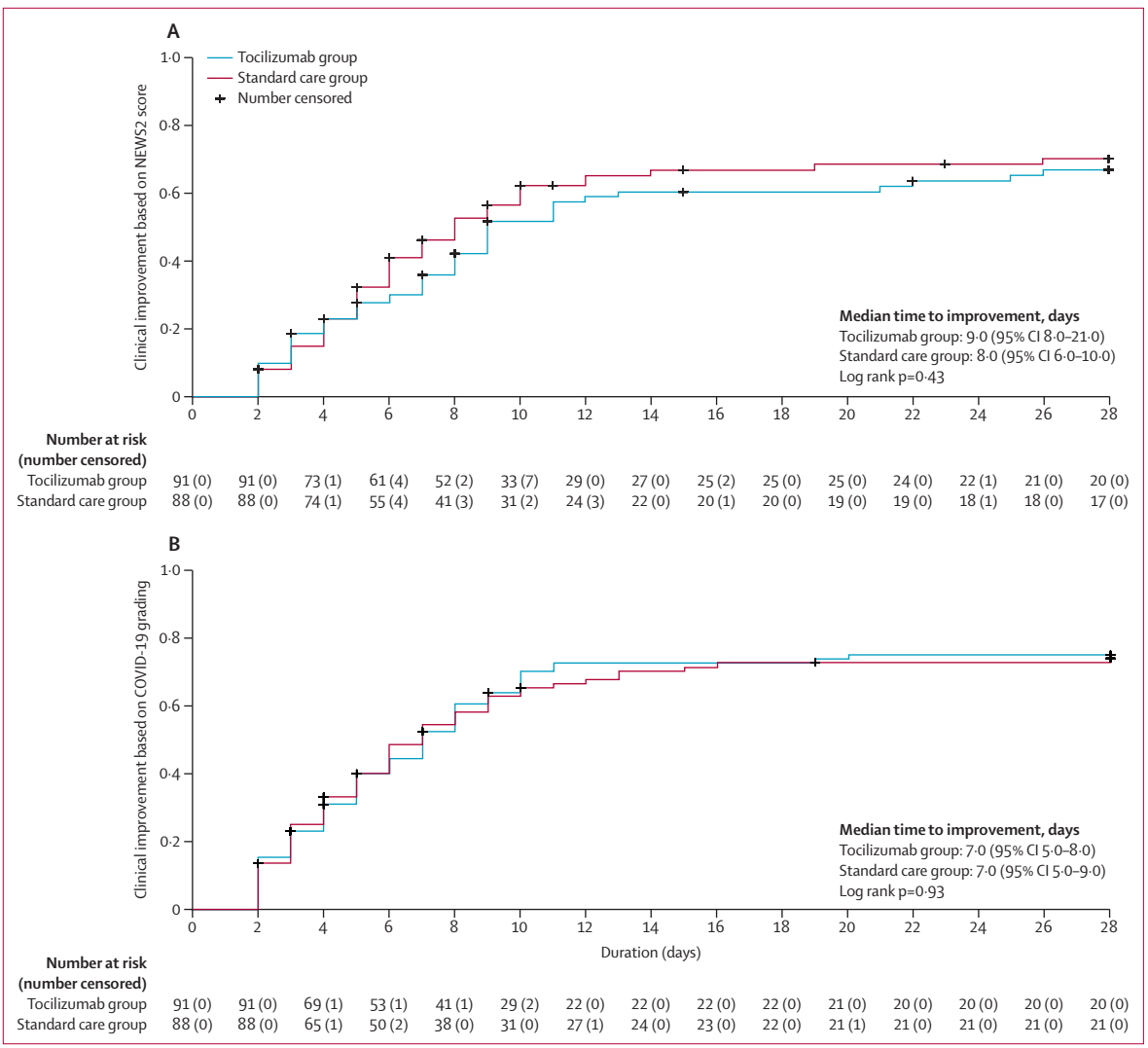

Figure 3: **Time to clinical improvement**
(A) Time to clinical improvement by NEWS2 maintained for 24 h and (B) time to clinical improvement by COVID-19 grading (modified intention-to-treat population). Median (95% CI) values were estimated using the Kaplan-Meier method, and p values were determined by log-rank test.

in the tocilizumab group and 13% (11 of 88) in the standard care group; the difference was not statistically significant (–3·71 [95% CI –18·23 to 11·19]; p=0·42; table 2, figure 2).

No significant difference was observed between the tocilizumab group and the standard care group in the secondary endpoints, including the proportion of patients with an at least one-grade improvement in cytokine release syndrome up to day 28, incidence of mechanical ventilation, ventilator-free days, organ failure-free days, incidence of ICU stay, duration of ICU stay, mortality, and supplemental oxygen-free days (table 2). One (1%) of 91 patients in the tocilizumab group and six (7%) of 88 patients in the standard care group required renal replacement therapy within 28 days. The proportions of patients with adverse events, serious adverse events, and post-treatment infections to day 28 were similar between the treatment groups. Kaplan-Meier analysis of time to clinical improvement by NEWS2 of 2 or less for 24 h up to day 28 and time to clinical improvement by COVID-19 grade did not show any statistical difference between the treatment groups (figure 3A, B). Serum IL-6 levels increased substantially in the tocilizumab group as expected when the IL-6 receptor is saturated with tocilizumab,[24] but not in the standard care group; median change from baseline to day 7 was 37·9 pg/mL (IQR –6·3 to 105·2) in the tocilizumab group and –4·3 pg/mL (–20·0 to 6·3) in the standard care group (p=0·0013). CRP and ferritin levels decreased in both treatment groups with no significant difference between the tocilizumab group and the standard care group in change from baseline to day 7 (table 2).

	Tocilizumab group (n=91)	Standard care group (n=89)
Adverse events	33 (36%)	22 (25%)
Infections	6 (7%)	5 (6%)
Serious adverse events*	18 (20%)	15 (17%)
Deaths	13 (14%)	15 (17%)
Grade 3 or worse adverse events	2 (2%)	5 (6%)
Serious adverse events by system organ class and preferred term		
Cardiac disorders	4 (4%)	3 (3%)
Acute coronary syndrome	1 (1%)	0
Acute left ventricular failure	0	1 (1%)
Arrythmia	1 (1%)	0
Bradycardia	1 (1%)	0
Cardiac arrest	0	2 (2%)
Myocarditis	1 (1%)	0
Gastrointestinal disorders (gastrointestinal haemorrhage)	1 (1%)	0
General disorders and administration-site conditions (all multiple organ dysfunction syndrome)	2 (2%)	5 (6%)
Infections and infestations (all sepsis)	3 (3%)	0
Nervous system disorders (seizure)	1 (1%)	0
Respiratory, thoracic, and mediastinal disorders	9 (10%)	7 (8%)
Acute respiratory distress syndrome	7 (8%)	7 (8%)
Pulmonary embolism	1 (1%)	0
Pulmonary fibrosis	1 (1%)	0
Vascular disorders	3 (3%)	8 (9%)
Hypertension	0	1 (1%)
Shock	3 (3%)	7 (8%)

Data are n (%). 54 adverse events (23 serious) occurred in 33 patients in the tocilizumab group and 55 adverse events (24 serious) occurred in 22 patients in the standard care group. System organ class and preferred term are according to the Medical Dictionary for Regulatory Activities, version 23.1. *Includes deaths (n=28), acute coronary syndrome (n=1), seizures (n=1), pulmonary embolism (n=1), colonic ulcer bleed (n=1), and pulmonary fibrosis (n=1).

Table 3: **All adverse events (safety population)**

54 adverse events were reported by 33 (36%) patients in the tocilizumab group, and 55 adverse events were reported by 22 (25%) patients in the standard care group (table 3). 13 (14%) patients in the tocilizumab group and 15 (17%) patients in the standard care group died during the study. Most adverse events were grade 1 or 2 in severity (30 [56%] of 54 events in the tocilizumab group and 20 [36%] of 55 events in the standard care group). Most events were considered unrelated to tocilizumab (45 [83%] of 54 events in the tocilizumab group). 23 serious adverse events were reported by 18 (20%) patients in the tocilizumab group and 24 were reported by 15 (17%) patients in the standard care group. The most frequently reported serious adverse events overall were acute respiratory distress syndrome, shock, cardiac disorders, and multiple organ dysfunction syndrome (table 3).

The proportions of patients who had disease progression up to day 28 were 12% (11 of 91) in the tocilizumab group and 18% (16 of 88) in the standard care group, with a difference of –6·09 (95% CI –20·73 to 8·79; p=0·25; figure 4A). Among the subset of patients who had severe COVID-19 at baseline, the proportions of patients who had disease progression (ie, died) up to day 28 were 16% (eight of 50) in the tocilizumab group and 34% (14 of 41) in the standard care group, with a difference of –18·15 (–37·79 to 2·43; p=0·044; figure 4A). The median time to disease progression or death to day 28 was not reached (ie, not evaluable; data for 37 patients who did not complete 28 days of follow-up and two patients who died after day 28 were censored at day 28) in the post-hoc analysis of all patients (figure 4B) or of those with severe COVID-19 at baseline (figure 4C). The log-rank p values for between-group comparisons were 0·25 overall and 0·04 for those with severe disease. Logistic regression analysis suggested that being older than 60 years and having severe COVID-19 were associated with higher mortality (appendix p 5).

Discussion

The COVINTOC trial was done to investigate whether tocilizumab, an anti-IL-6 receptor antibody, might be able to address the unmet medical need for effective treatment of patients admitted to hospital with COVID-19 in India. The primary and secondary endpoints were not significantly different between tocilizumab plus standard care and standard care alone. Thus, our study does not support the routine use of tocilizumab in adults with COVID-19. Safety results were as expected on the basis of the known safety profile of tocilizumab and the disease manifestations of patients admitted to hospital with COVID-19. Post-hoc analyses suggested that patients with severe disease at baseline (as classified by the Indian MoHFW), most of whom were not on mechanical ventilation, might have a reduced risk for progression to death if treated with tocilizumab in addition to standard care; however, clinical parameters or biomarkers to reliably identify these patients and the optimal timing of treatment during COVID-19 progression remain unknown.

Conducting robust clinical trials during the COVID-19 pandemic is impeded by challenges such as there being no established standard care, administration of off-label treatments, rapidly evolving understanding of pathogenesis and treatment, multiple trials competing for participants, media hype, and the publication of non-peer-reviewed reports. Additional barriers to conducting multicentre clinical trials in India, a large and low-resource country, are absence of a robust state health system, sparse allocation of research funds, drug scarcities, logistical challenges, travel restrictions, reluctance or inability of patients who have recovered from COVID-19 to travel back to sites for follow-up visits, and shortages in research staff because the risk for contracting

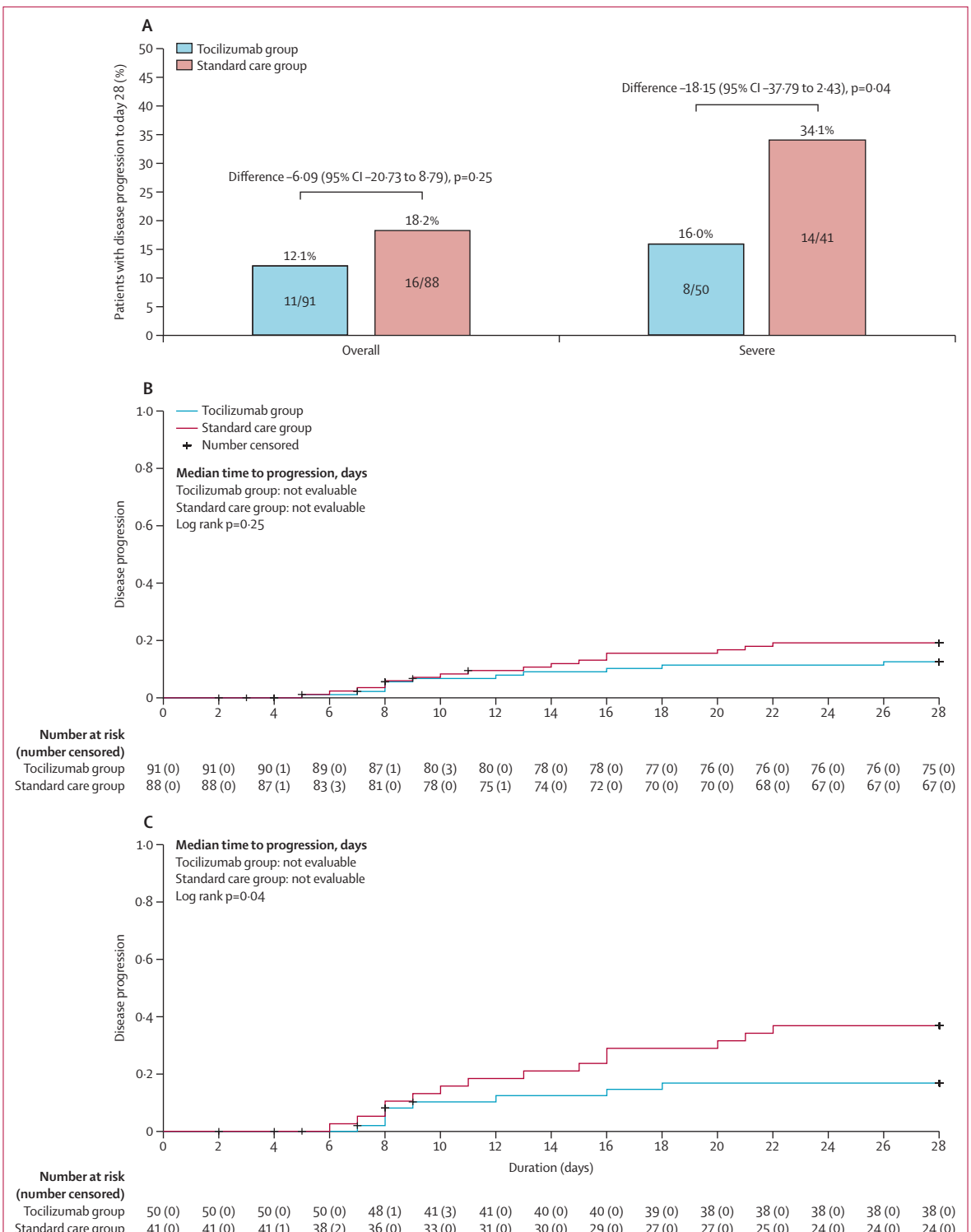

Figure 4: **COVID-19 progression post-hoc analyses**

(A) Proportions of patients with COVID-19 progression up to day 28. Time to progression of COVID-19 up to day 28 among all patients (B) and among those with severe disease at baseline (C). Median time to progression was not evaluable for 37 patients who did not complete 28 days of follow-up or who died after day 28, and data were censored for these patients (B, C).

SARS-CoV-2 is high and personnel are deployed for active clinical care in already overstretched systems. Challenges to conducting randomised controlled trials during the COVID-19 pandemic are exacerbated in LMICs, and several hurdles were encountered during this trial in India. Off-label or compassionate use of treatments in patients with COVID-19 is common during this pandemic and can impede enrolment into clinical trials. Ensuring follow-up is challenging for patients who are likely to be discharged early because of the high demand on hospital resources and for patients who might have logistical difficulty travelling for return visits. Furthermore, research staff are limited by stretched resources and because personnel involved in the trial put themselves at risk for SARS-CoV-2 infection, presenting a potential burden of disease on staff and their families. We have demonstrated that, even during a pandemic, it is possible to conduct a randomised controlled trial despite the multiple challenges and constraints encountered in India. We believe it is important that all potential therapies be trialled across diverse settings, not only in North America and Europe.

Four other randomised controlled trials of tocilizumab in patients admitted to hospital with COVID-19 were completed after our trial was initiated. Tocilizumab did not improve clinical status or mortality beyond standard care in the global randomised controlled COVACTA trial of patients admitted to hospital with severe COVID-19 pneumonia, but potential benefits in time to hospital discharge and duration of ICU stay were identified (non-peer reviewed article).[15] Another global randomised controlled trial that enrolled patients who were admitted to hospital with COVID-19 pneumonia but not on mechanical ventilation—particularly those from high-risk and minority populations—showed that tocilizumab plus standard care reduced the risk for mechanical ventilation or death compared with standard care alone.[16] This is similar to the observations of our post-hoc analysis in which patients with severe disease at baseline who received tocilizumab in addition to standard care had a survival benefit at 28 days. Another randomised controlled trial done in the USA did not show a benefit for tocilizumab in preventing intubation or death in patients admitted to hospital with COVID-19,[17] and an open-label randomised trial done in France found no effect of tocilizumab on clinical status or mortality at 28 days, but that study did suggest that there might be a reduced risk for non-invasive ventilation, mechanical ventilation, or death at day 14.[18]

The strengths of our study are that it was a randomised controlled trial of tocilizumab done in a population with a high unmet need for COVID-19 treatments. Study sites were located across India and included private and public hospitals, ensuring broad patient representation. To date, it is also the only completed and published randomised controlled trial in patients with COVID-19 conducted entirely in an LMIC. Although the primary and secondary outcomes were not met, post-hoc analyses revealed a subset of patients with severe disease in whom tocilizumab might reduce mortality. This information could help limit the scientifically unsubstantiated routine use of tocilizumab in all patients admitted to hospital with COVID-19 in resource-constrained countries such as India. Limitations of our study include the fact that it was an unmasked study with no placebo. Most patients received concomitant corticosteroids during the trial, and about half received antiviral therapy with remdesivir. The use of concomitant medications in these patients could have muted any beneficial effect that tocilizumab might otherwise have had. Another limitation is that the number of patients who were initially considered by the investigators but were not screened is unknown because this information was not collected given the challenges of rapidly recruiting patients during the pandemic. Nevertheless, all patients who consented did undergo formal screening. The sample size was decided on the basis of an assumption of significant improvement despite the absence of any such finding in the literature, and the study was not powered to detect a small difference despite the relatively large sample size. It is possible that a larger sample size would be needed to establish a difference between treatment groups. Additionally, clinical criteria (ie, definitions) for moderate and severe disease might have been influenced by subjectivity. The clinical endpoint (progression of disease) might therefore reflect this influence, but similar results observed in both treatment groups eliminate the possibility of such bias.

In conclusion, our study does not support the routine use of tocilizumab in adults with COVID-19. However, there might be a role for it in patients with severe COVID-19 that should be defined further.

Contributors

ASS, KK, NSC, PS, and AVR contributed to the literature search, protocol development, study steering committee, study design, data analysis, data interpretation, and writing of the manuscript. YM, SK, DG, VD, DC, PKS, AG, VA, SK, SAS, RC, SN, RP, VM, and MG contributed to data collection, conduct of the study, resolution of data quality and queries, and critical review of the manuscript. ASS and AVR verify that they had access to and take responsibility for all the data in the manuscript. ASS, KK, NSC, PS, and AVR had access to the raw data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AVR reports personal speaker fees, honoraria, and advisory board fees from Roche outside of the submitted work and is a member of the paediatric steering committee of the RECOVERY trial. All other authors declare no competing interests.

Acknowledgments

The first draft of the manuscript was prepared by ASS, KK, NSC, PS, and AVR, with writing support provided by Sara Duggan, of ApotheCom. JSS Medical Research India (a contract research organisation) supported monitoring and logistics at all sites as well as statistical analysis for the study. The study was funded by the Medanta Institute of Education and Research (MIER), partly from its own funds and partly from unrestricted grants it received from Cipla and Roche Products (India) and from Action COVID-19 Team, India. The MIER constituted the study steering committee, which closely monitored the design and conduct of the study

and appointed an independent drug and safety monitoring board. Four MIER scientists are among the authors of this paper and were involved in writing the report. The investigational medicinal product (tocilizumab) was supplied by Cipla and Roche Products (India) Pvt Ltd, which also provided an unrestricted grant for the study. We thank Dr Naresh Trehan, Managing Trustee of MIER, for help and guidance of the steering committee and for logistics and funding sources. We especially thank the patients and their families who participated in this trial in such a challenging situation as the COVID-19 pandemic and thank the Central Drugs Standard Control Organisation for their expedited and expert review of research protocols, which allowed the trial to proceed efficiently during unprecedented circumstances.

Data sharing

Data collected for the study, including deidentified participant data and related documents, including the protocol, statistical analysis plan, and informed consent form, will be made available to qualified researchers after publication of the manuscript upon reasonable request via application to the corresponding author (ASS).

References

1 Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med* 2020; published online July 17. https://doi.org/10.1056/NEJMoa2021436.

2 Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. *N Engl J Med* 2020; **383:** 1813–26.

3 Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020; **324:** 782–93.

4 Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe* 2020; **27:** 992–1000.e3.

5 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; **382:** 1708–20.

6 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323:** 1239–42.

7 Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents* 2020; **34:** 327–31.

8 Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. *J Med Virol* 2020; **92:** 2283–85.

9 Zhu J, Pang J, Ji P, et al. Elevated interleukin-6 is associated with severity of COVID-19: a meta-analysis. *J Med Virol* 2020; published online May 29. https://doi.org/10.1002/jmv.26085.

10 Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; **46:** 846–48.

11 Rubbert-Roth A, Furst DE, Nebesky JM, Jin A, Berber E. A review of recent advances using tocilizumab in the treatment of rheumatic diseases. *Rheumatol Ther* 2018; **5:** 21–42.

12 Antwi-Amoabeng D, Kanji Z, Ford B, Beutler BD, Riddle MS, Siddiqui F. Clinical outcomes in COVID-19 patients treated with tocilizumab: an individual patient data systematic review. *J Med Virol* 2020; **92:** 2516–22.

13 Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA* 2020; **117:** 10970–75.

14 Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol* 2020; **92:** 814–18.

15 Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. *medRxiv* 2020; published online Sept 12. https://doi.org/10.1101/2020.08.27.20183442 (preprint).

16 Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med* 2021; **384:** 20–30.

17 Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med* 2020; **383:** 2333–44.

18 Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021; **181:** 32–40.

19 Sharma P, Chowdhury AR. Challenges and dilemmas of operationalizing COVID-19 clinical research in India. August, 2020. https://globalforum.diaglobal.org/issue/august-2020/challenges-and-dilemmas-of-operationalizing-covid-19-clinical-research-in-india/ (accessed Nov 19, 2020).

20 Ministry of Health and Family Welfare, Directorate General of Health Services, EMR Division. Guidance document on appropriate management of suspect/confirmed cases of COVID-19. April 7, 2020. https://www.mohfw.gov.in/pdf/FinalGuidanceonMangaementofCovidcasesversion2.pdf (accessed Nov 19, 2020).

21 National Health Comission & National Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7). *Chin Med J* 2020; **133:** 1087–95.

22 Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant* 2019; **25:** 625–38.

23 National Cancer Institute. Common terminology criteria for adverse events (CTCAE) version 4.0. May 28, 2009. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (accessed Nov 19, 2020).

24 Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood* 2008; **112:** 3959–64.