Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

*RECOVERY Collaborative Group**

Summary

Background In this study, we aimed to evaluate the effects of tocilizumab in adult patients admitted to hospital with COVID-19 with both hypoxia and systemic inflammation.

Methods This randomised, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), is assessing several possible treatments in patients hospitalised with COVID-19 in the UK. Those trial participants with hypoxia (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein ≥75 mg/L) were eligible for random assignment in a 1:1 ratio to usual standard of care alone versus usual standard of care plus tocilizumab at a dose of 400 mg–800 mg (depending on weight) given intravenously. A second dose could be given 12–24 h later if the patient's condition had not improved. The primary outcome was 28-day mortality, assessed in the intention-to-treat population. The trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

Findings Between April 23, 2020, and Jan 24, 2021, 4116 adults of 21 550 patients enrolled into the RECOVERY trial were included in the assessment of tocilizumab, including 3385 (82%) patients receiving systemic corticosteroids. Overall, 621 (31%) of the 2022 patients allocated tocilizumab and 729 (35%) of the 2094 patients allocated to usual care died within 28 days (rate ratio 0·85; 95% CI 0·76–0·94; p=0·0028). Consistent results were seen in all prespecified subgroups of patients, including those receiving systemic corticosteroids. Patients allocated to tocilizumab were more likely to be discharged from hospital within 28 days (57% *vs* 50%; rate ratio 1·22; 1·12–1·33; p<0·0001). Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (35% *vs* 42%; risk ratio 0·84; 95% CI 0·77–0·92; p<0·0001).

Interpretation In hospitalised COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes. These benefits were seen regardless of the amount of respiratory support and were additional to the benefits of systemic corticosteroids.

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*The writing committee and trial steering committee are listed at the end of this manuscript and a complete list of collaborators in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is provided in the appendix (pp 2–25)

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See **Online** for appendix

Introduction

The majority of SARS-CoV-2 infections are either asymptomatic or result in only mild disease.[1] However, a substantial proportion of infected individuals develop a respiratory illness requiring hospital care, which can progress to critical illness with hypoxic respiratory failure requiring prolonged ventilatory support. Among COVID-19 patients admitted to UK hospitals in spring, 2020, the case fatality rate was over 26%, and was in excess of 37% in patients requiring invasive mechanical ventilation.[2]

Hypoxic respiratory failure in patients with COVID-19 is associated with evidence of systemic inflammation, including release of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumour necrosis factor α, and elevated concentrations of D-dimer, ferritin, and C-reactive protein (CRP).[3,4] The host immune response is thought to play a key role in driving an acute inflammatory pneumonic process with diffuse alveolar damage, myeloid cell infiltrates, and microvascular thrombosis.[5] The beneficial effects of dexamethasone and other corticosteroids in COVID-19 patients with hypoxic lung damage suggest that other, more specific, immunomodulatory agents might provide additional improvements in clinical outcomes.[6,7]

Tocilizumab is a recombinant humanised anti-IL-6 receptor monoclonal antibody that inhibits the binding of IL-6 to both membrane and soluble IL-6 receptors, blocking IL-6 signalling and reducing inflammation. Tocilizumab is licensed in the UK as an intravenous treatment for patients with rheumatoid arthritis and for people with chimeric antigen receptor T-cell-induced severe or life-threatening cytokine release syndrome. Randomised trials of tocilizumab in COVID-19 have so far shown mixed results for 28-day mortality: seven small trials reported no benefit and the somewhat larger

Research in context

Evidence before this study

We searched MEDLINE, Embase, and MedRxiv from inception up to March 5, 2021, for clinical trials or meta-analyses evaluating the effect of interleukin-6 inhibitor treatment on patients with COVID-19 using the search terms ("COVID-19" OR "COVID" OR "SARS-CoV-2" OR "2019-nCoV" OR "coronavirus") AND ("tocilizumab" OR "sarilumab" OR "interleukin-6 inhibitor" or "IL-6 inhibitor").

We identified eight relevant randomised trials that compared tocilizumab with usual care or placebo in hospitalised patients with COVID-19. All were assessed as at low risk of bias. Of these trials, only the REMAP-CAP trial in critically ill patients found a significant reduction in 28-day mortality with tocilizumab. A meta-analysis of these eight trials, which included a total of 439 deaths among 2379 patients showed no significant difference in 28-day mortality (death rate ratio 0·89, 95% CI 0·72–1·11).

Added value of this study

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is the largest randomised trial of the effect of tocilizumab in hospitalised patients with COVID-19. We found that in 4116 COVID-19 patients with hypoxia and a raised C-reactive protein, tocilizumab reduced 28-day mortality, increased the probability of discharge within 28 days, and, among patients who were not receiving invasive mechanical ventilation at randomisation, reduced the probability of progression to the composite outcome of invasive mechanical ventilation or death. The benefits were in addition to corticosteroids and consistent in all subgroups, regardless of the amount of respiratory support.

Implications of all the available evidence

Our finding shows that tocilizumab improves survival and other clinical outcomes in a broad group of patients hospitalised with COVID-19 and that these benefits are additional to those of corticosteroids.

REMAP-CAP trial reported a benefit in patients requiring organ support.[8–15] Here we report the results of a large randomised, controlled trial aimed at evaluating the effects of tocilizumab in adult patients hospitalised with severe COVID-19 characterised by hypoxia and substantial inflammation.

Methods

Study design and participants

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an investigator-initiated, individually randomised, controlled, open-label, platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19. Details of the trial design and results for other possible treatments have been published previously.[6,16–18] The trial is being done in acute National Health Service hospitals in the UK, supported by the National Institute for Health Research Clinical Research Network (appendix pp 2–25). The trial is coordinated by the Nuffield Department of Population Health at University of Oxford (Oxford, UK), the trial sponsor. The trial is being done in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines and is approved by the UK Medicines and Healthcare products Regulatory Agency and the Cambridge East Research Ethics Committee. The protocol, statistical analysis plan, and additional information are available on the study website. This report is limited to adult patients. The randomised assessment of tocilizumab in children younger than 18 years is ongoing.

For more on the **RECOVERY trial** see www.recoverytrial.net

Patients admitted to hospital were eligible for the study if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at substantial risk if they were to participate in the trial. Written informed consent was obtained from all patients, or their legal representative if they were too unwell or unable to provide consent.

Randomisation and masking

Data were collected at study entry using a web-based case report form that included demographics and major comorbidities (appendix p 32). All eligible and consenting patients received usual standard of care and underwent an initial (main) randomisation comprising up to three parts in a factorial design (appendix pp 29–30): part 1, no additional treatment versus either dexamethasone, lopinavir–ritonavir, hydroxychloroquine, azithromycin, or colchicine; part 2, no additional treatment versus either convalescent plasma or REGN-COV2 (a combination of two monoclonal antibodies directed against SARS-CoV-2 spike protein); and part 3, no additional treatment versus aspirin. Over time, treatment groups were added to and removed from the protocol (appendix pp 26–29), and not all treatments were available at every hospital. Similarly, not all treatments were suitable for some patients (eg, owing to comorbid conditions or concomitant medication). In any of these cases, randomisation was between fewer groups.

Up to 21 days after the main randomisation and regardless of treatment allocation, RECOVERY trial participants with clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L) could be considered for randomisation to tocilizumab versus usual care alone. Baseline data collected for this randomisation included amount of respiratory support, markers of progressive COVID-19 (including most recent oxygen saturation, CRP, ferritin, and creatinine result

before second randomisation), suitability for the study treatment, and treatment availability at the site (appendix pp 33–34). For some patients, tocilizumab was unavailable at the hospital at the time of enrolment or was considered by the managing physician to be either definitely indicated or definitely contraindicated. In such cases, the patients were not eligible for the tocilizumab randomisation. Patients with known hypersensitivity to tocilizumab, evidence of active tuberculosis infection or clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19) were not eligible for randomisation to tocilizumab.

Patients who were eligible for randomisation to tocilizumab were assigned to either usual standard of care or usual standard of care plus tocilizumab in a 1:1 ratio by means of web-based simple (unstratified) randomisation with allocation concealed until after randomisation. Allocated treatment was prescribed by the managing doctor. Roche Products (Welwyn Garden City, UK) supported the trial through provision of tocilizumab. Participants and local study staff were not masked to the allocated treatment. The steering committee, investigators, and all others involved in the trial were masked to the outcome data during the trial.

Procedures

Patients allocated to tocilizumab were to receive tocilizumab as a single intravenous infusion over 60 min. The dose of tocilizumab was established by bodyweight (800 mg if weight >90 kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8 mg/kg if weight ≤40 kg). A second dose could be given 12–24 h later if, in the opinion of the attending clinician, the patient's condition had not improved.

A single online follow-up form was completed when participants were discharged, had died, or at 28 days after

	Tocilizumab group (n=2022)	Usual care group (n=2094)
Age, years	63·3 (13·7)	63·9 (13·6)
≥18 to <70	1331 (66%)	1355 (65%)
≥70 to <80	478 (24%)	480 (23%)
≥80	213 (11%)	259 (12%)
Sex		
Male	1337 (66%)	1437 (69%)
Female*	685 (34%)	657 (31%)
Ethnicity		
White	1530 (76%)	1597 (76%)
Black, Asian, or minority ethnic	354 (18%)	378 (18%)
Unknown	138 (7%)	119 (6%)
Number of days since symptom onset	9 (7–13)	10 (7–14)
Number of days since hospitalisation	2 (1–5)	2 (1–5)
Oxygen saturation	94% (92–96)	94% (91–95)
Respiratory support at second randomisation		
No ventilator support†	935 (46%)	933 (45%)
Non-invasive ventilation‡	819 (41%)	867 (41%)
Invasive mechanical ventilation§	268 (13%)	294 (14%)
Biochemistry at second randomisation		
Latest C-reactive protein, mg/L	143 (107–203)	144 (106–205)
Ferritin, ng/mL	947 (497–1599)	944 (507–1533)
Creatinine, μmol/L	77 (62–98)	77 (62–100)
Previous diseases		
Diabetes	569 (28%)	600 (29%)
Heart disease	435 (22%)	497 (24%)
Chronic lung disease	473 (23%)	484 (23%)
Tuberculosis	3 (<1%)	5 (<1%)
HIV	7 (<1%)	8 (<1%)
Severe liver disease¶	14 (1%)	10 (<1%)
Severe kidney impairment‖	118 (6%)	99 (5%)
Any of the above	1100 (54%)	1163 (56%)

(Table 1 continues in next column)

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	Tocilizumab group (n=2022)	Usual care group (n=2094)
SARS-CoV-2 test result		
Positive	1922 (95%)	2005 (96%)
Negative	69 (3%)	71 (3%)
Not known	31 (2%)	18 (1%)
First randomisation**		
Number of days since first randomisation	0 (0–1)	0 (0–1)
Part A allocation		
Usual care	839 (41%)	869 (41%)
Lopinavir–ritonavir	51 (3%)	64 (3%)
Dexamethasone	49 (2%)	45 (2%)
Hydroxychloroquine	37 (2%)	38 (2%)
Azithromycin	197 (10%)	177 (8%)
Use of systemic corticosteroids††		
Yes	1664 (82%)	1721 (82%)
No	357 (18%)	367 (18%)
Unknown	1 (<1%)	6 (<1%)

Data are mean (SD), n (%), or median (IQR). Information on sex, ethnicity, and SARS-CoV-2 test result were recorded on the main randomisation form when patients first entered the study. All other information was recorded on the second randomisation form (when patients were randomly assigned to tocilizumab *vs* usual care alone). *Includes ten pregnant women. †Includes nine patients not receiving any oxygen and 1859 patients receiving low-flow oxygen. ‡Includes patients receiving high-flow nasal oxygen, continuous positive airway pressure, or other non-invasive ventilation. §Includes patients receiving invasive mechanical ventilation or extracorporeal membranous oxygenation. ¶Defined as requiring ongoing specialist care. ‖Defined as estimated glomerular filtration rate <30 mL/min per 1·73 m^2. **2631 participants were randomly assigned into part B and 1615 into part C of the first randomisation. ††Information on use of corticosteroids was collected from June 18, 2020, onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. Participants undergoing first randomisation before this date (and who were not allocated to dexamethasone) are assumed not to be receiving systemic corticosteroids.

Table 1: **Baseline characteristics**

the initial randomisation, whichever occurred earliest (appendix pp 35–41). Information was recorded on adherence to allocated study treatment, receipt of other COVID-19 treatments, duration of admission, receipt of respiratory or renal support, and vital status (including cause of death). In addition, routine health-care and registry data were obtained for the full follow-up period, including information on vital status (with date and cause of death), discharge from hospital, receipt of respiratory support, or renal replacement therapy.

Outcomes

Outcomes were assessed at 28 days after randomisation to tocilizumab versus usual care alone, with further analyses specified at 6 months. The primary outcome was all-cause mortality. Secondary outcomes were time to discharge from hospital, and, among patients not receiving invasive mechanical ventilation at randomisation, receipt of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Prespecified subsidiary clinical outcomes were use of non-invasive respiratory support (defined as high-flow nasal oxygen, continuous positive airway pressure, or non-invasive ventilation), time to successful cessation of invasive mechanical ventilation (defined as cessation of invasive mechanical ventilation within, and survival to, 28 days), and use of renal dialysis or haemofiltration. Prespecified safety outcomes included cause-specific mortality and major cardiac arrhythmia. Information on suspected serious adverse reactions was collected in an expedited fashion to comply with regulatory requirements.

Statistical analysis

In accordance with the statistical analysis plan (version 2.1, appendix pp 93–117), an intention-to-treat comparison was done between patients who entered the randomised comparison of tocilizumab versus usual care. For the primary outcome of 28-day mortality, the log-rank observed minus expected statistic and its variance were used to test the null hypothesis of equal survival curves (ie, the log-rank test) and to calculate the one-step estimate of the average mortality rate ratio. We

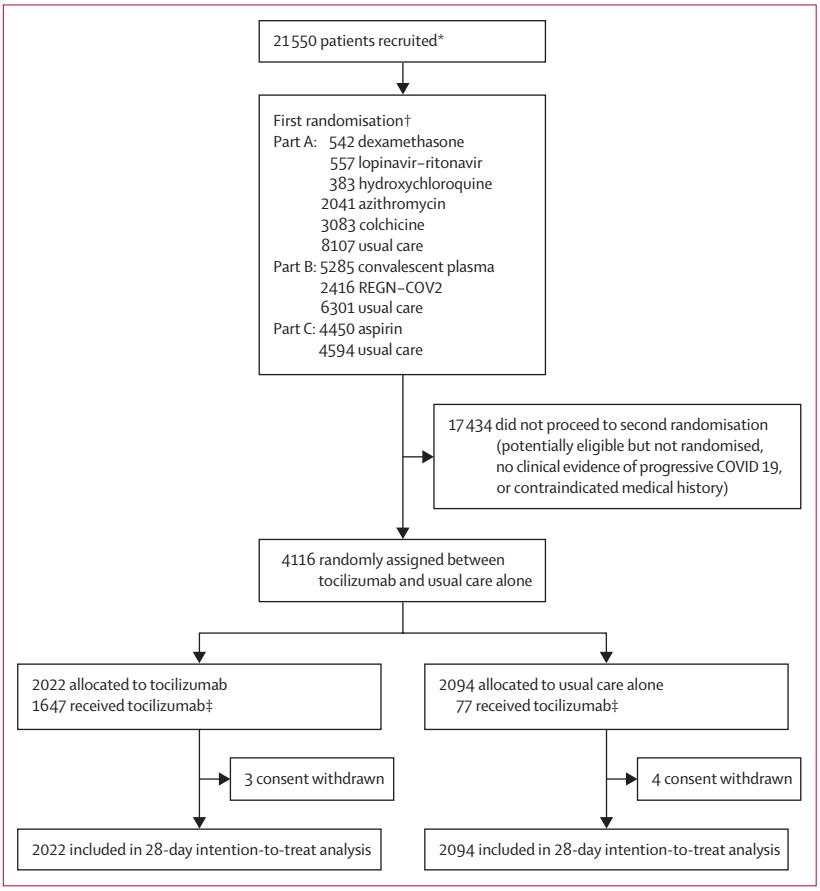

Figure 1: **Trial profile**
REGN-COV2=a combination of two monoclonal antibodies directed against SARS-CoV-2 spike protein. *Number of adult patients recruited at a site activated for the tocilizumab comparison. †The first randomisation comprised up to three factorial elements such that an eligible patient could be entered into between one and three randomised comparisons, depending on the then current protocol, the patient's suitability for particular treatments, and the availability of the treatment at the site. Median time between first and second randomisation was 0·3 h (IQR 0·1–25·3). ‡1964 (97%) of 2022 patients of those allocated to tocilizumab and 2049 (98%) of 2094 of those allocated to usual care had a completed follow-up form at time of analysis.

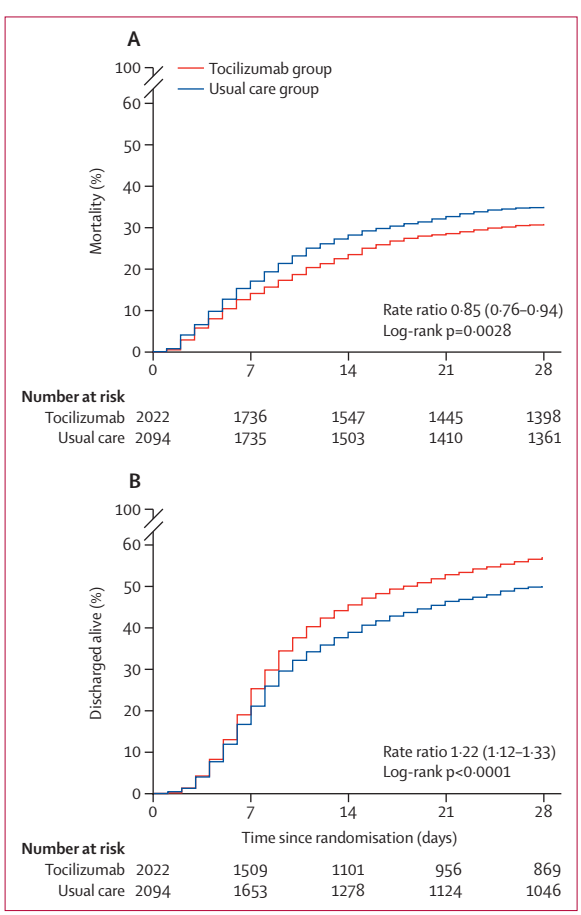

Figure 2: **Effect of allocation to tocilizumab on 28-day mortality (A) and discharge from hospital within 28 days of randomisation (B)**

constructed Kaplan-Meier survival curves to display cumulative mortality over the 28-day period. We used the same method to analyse time to hospital discharge and successful cessation of invasive mechanical ventilation, with patients who died in hospital right-censored on day 29. For the prespecified composite secondary outcome of invasive mechanical ventilation or death within 28 days (among those not receiving invasive mechanical ventilation at randomisation) and the subsidiary clinical outcomes of receipt of ventilation and receipt of haemodialysis or haemofiltration, the precise dates were not available and so the risk ratio was estimated instead.

Prespecified analyses of the primary outcome were done in subgroups defined by six characteristics at the time of randomisation: age, sex, ethnicity, amount of respiratory support, days since symptom onset, and use of systemic corticosteroids (including dexamethasone). Observed effects within subgroup categories were compared by means of a χ^2 test for heterogeneity or trend, in accordance with the prespecified analysis plan.

Estimates of rate and risk ratios are shown with 95% CIs. All p values are two-sided and are shown without adjustment for multiple testing. The full database is held by the study team which collected the data from study sites and did the analyses at the Nuffield Department of Population Health, University of Oxford (Oxford, UK).

Before commencement of the randomisation to tocilizumab versus usual care, the trial steering committee determined that if 28-day mortality in the usual care group was above 25% then recruitment of around 4000 patients to this comparison would provide 90% power at two-sided p=0·01 to detect a proportional reduction in 28-day mortality of one-fifth. Consequently, Roche Products provided sufficient treatment for 2000 patients to receive tocilizumab. The trial steering committee, masked to the results, closed recruitment to the tocilizumab comparison at the end of Jan 24, 2021, as over 4000 patients had been randomly assigned.

For the primary outcome of 28-day mortality, the results from RECOVERY were subsequently included in a meta-analysis of results from all previous randomised trials of tocilizumb versus usual care in patients with COVID-19. For each trial, we compared the observed number of deaths among patients allocated tocilizumab with the expected number if all patients were at equal risk (ie, we calculated the observed minus expected statistic [o–e], and its variance v). For RECOVERY, these were taken as the log-rank observed minus expected statistic and its variance but for other trials, where the exact timing of each death was not available, these were calculated from standard formulae for 2×2 contingency tables. We then combined trial results using the log of the mortality rate ratio calculated as the inverse-variance weighted average S/V with variance 1/V (and hence with 95% CI S/V ±1·96/√V), where S is the sum over all trials of (O–E) and V is the sum over all trials of v.[19] Analyses were done by means of SAS version 9.4 and R version 3.4. The trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

Role of the funding source

Neither the funders of the study nor Roche Products had any role in study design, data collection, data analysis, data interpretation, or writing of the report. Roche Products supported the study through the supply of tocilizumab and reviewed the draft publication for factual accuracy relating to tocilizumab.

Results

Between April 23, 2020, and Jan 24, 2021, 4116 (19%) of 21550 patients enrolled into the RECOVERY trial at one of the 131 sites in the UK participating in the tocilizumab comparison were eligible for random assignment. 2022 patients were randomly allocated to tocilizumab and 2094 were randomly allocated to usual care. The mean age of these participants was 63·6 years (SD 13·6). At randomisation, 562 (14%) of 4116 patients were receiving invasive mechanical ventilation, 1686 (41%) of 4116 were receiving non-invasive respiratory support (including high-flow nasal oxygen, continuous positive airway pressure, and non-invasive ventilation), and 1868 (45%) of

	Treatment allocation		RR (95% CI)	p value
	Tocilizumab group (n=2022)	Usual care group (n=2094)		
Primary outcome				
28-day mortality	621 (31%)	729 (35%)	0·85 (0·76–0·94)	0·0028
Secondary outcomes				
Median time to being discharged, days	19	>28	..	..
Discharged from hospital within 28 days	1150 (57%)	1044 (50%)	1·22 (1·12–1·33)	<0·0001
Receipt of invasive mechanical ventilation or death*	619/1754 (35%)	754/1800 (42%)	0·84 (0·77–0·92)	<0·0001
Invasive mechanical ventilation	265/1754 (15%)	343/1800 (19%)	0·79 (0·69–0·92)	0·0019
Death	490/1754 (28%)	580/1800 (32%)	0·87 (0·78–0·96)	0·0055
Subsidiary clinical outcomes				
Receipt of ventilation†	290/935 (31%)	323/933 (35%)	0·90 (0·79–1·02)	0·10
Non-invasive ventilation	281/935 (30%)	309/933 (33%)	0·91 (0·79–1·04)	0·15
Invasive mechanical ventilation	67/935 (7%)	86/933 (9%)	0·78 (0·57–1·06)	0·11
Successful cessation of invasive mechanical ventilation‡	95/268 (35%)	98/294 (33%)	1·08 (0·81–1·43)	0·60
Use of haemodialysis or haemofiltration§	120/1994 (6%)	172/2065 (8%)	0·72 (0·58–0·90)	0·0046

Data are n (%), n/N (%), or median (IQR) unless stated otherwise. RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. *Analyses include only those on no ventilator support or non-invasive ventilation at second randomisation. †Analyses include only those on no ventilator support at second randomisation. ‡Analyses restricted to those on invasive mechanical ventilation at second randomisation. §Analyses exclude those on haemodialysis or haemofiltration at second randomisation.

Table 2: **Effect of allocation to tocilizumab on main study outcomes**

4116 were receiving no respiratory support other than simple oxygen therapy (nine of these patients were reportedly not receiving oxygen at randomisation; table 1). Median CRP was 143 (IQR 107–204) mg/L. 82% of patients were reported to be receiving corticosteroids at randomisation (and 97% of the patients enrolled since the announcement of the dexamethasone result from RECOVERY in June, 2020).

The follow-up form was completed for 1964 (97%) of 2022 randomly assigned patients in the tocilizumab group and 2049 (98%) of 2094 patients in the usual care group. Among patients with a completed follow-up form, 1647 (84%) of 1964 allocated to tocilizumab and 77 (4%) of 2049 of those allocated to usual care received at least one dose of tocilizumab (or sarilumab, another IL-6 antagonist; figure 1; appendix p 44). 565 (29%) of 1964 patients in the tocilizumab group and 17 (1%) of 2049 in the usual care group received more than one dose of tocilizumab (or sarilumab). Use of other treatments for COVID-19 during the 28 days after randomisation was similar among patients allocated tocilizumab and among those allocated usual care (appendix p 44). Follow-up for the primary and secondary outcomes was complete for 99% of randomised participants.

Allocation to tocilizumab was associated with a significant reduction in the primary outcome of 28-day mortality compared with usual care alone (621 [31%] of 2022 patients in the tocilizumab group *vs* 729 (35%) of 2094 patients in the usual care group; rate ratio 0·85; 95% CI, 0·76–0·94; p=0·0028; figure 2A). In an exploratory analysis restricted to the 3927 (95%) patients with a positive SARS-CoV-2 test result, the result was similar (rate ratio 0·86, 95% CI 0·77–0·97; p=0·0098).

Allocation to tocilizumab was associated with a greater probability of discharge from hospital within 28 days (57% *vs* 50%; rate ratio 1·22, 1·12–1·33, p<0·0001; figure 2B and table 2). Among those not on invasive mechanical ventilation at baseline, allocation to tocilizumab was associated with a reduction in the risk of progressing to the prespecified composite secondary outcome of invasive mechanical ventilation or death when compared with usual care alone (35% *vs* 42%, risk ratio 0·84, 0·77–0·92, p<0·0001; table 2).

We observed similar results across all prespecified subgroups (figure 3, appendix pp 48–49), including the

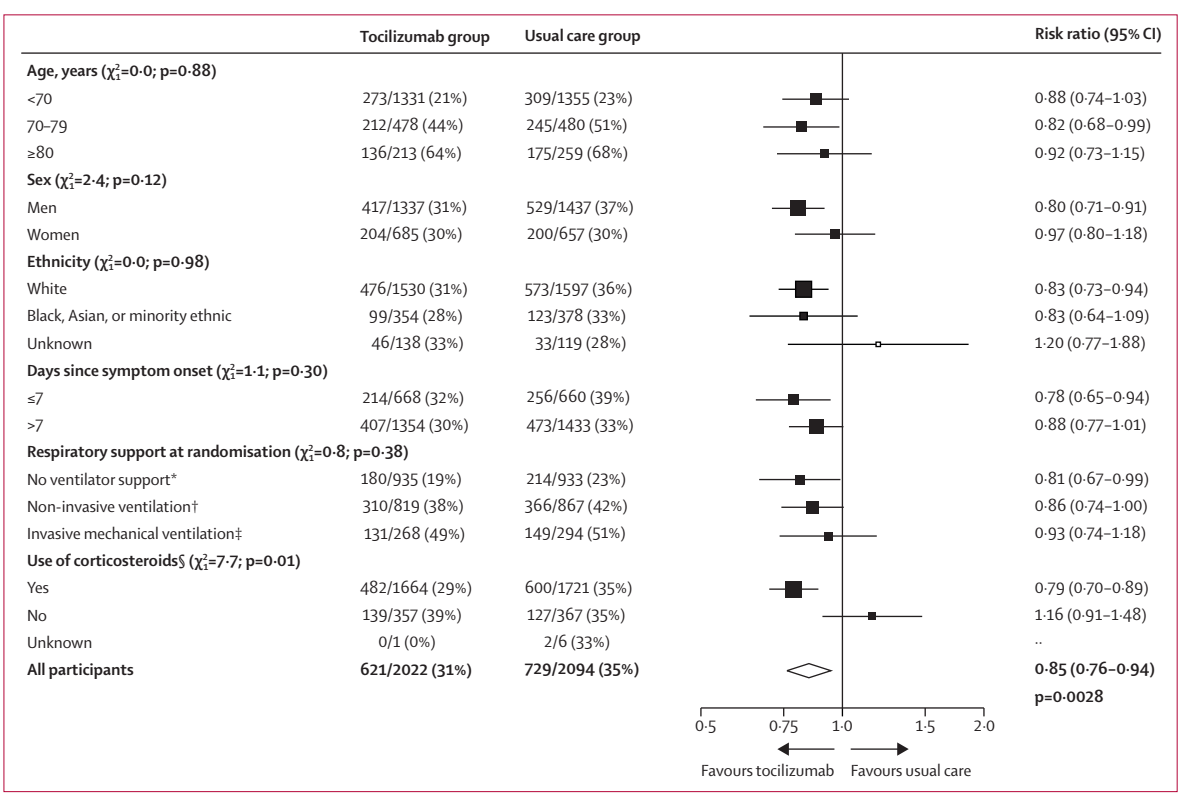

Figure 3: **Effect of allocation to tocilizumab on 28-day mortality by baseline characteristics**

Subgroup-specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. *Includes nine patients not receiving any oxygen and 1859 patients receiving simple oxygen only. †Includes patients receiving high-flow nasal oxygen, continuous positive airway pressure ventilation, and other non-invasive ventilation. ‡Includes patients receiving invasive mechanical ventilation and extracorporeal membranous oxygenation. §Information on use of corticosteroids was collected from June 18, 2020, onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. Participants undergoing first randomisation before this date (and who were not allocated to dexamethasone) are assumed not to be receiving systemic corticosteroids. In a model adjusted for all six baseline subgroups (in the categories shown) the overall rate ratio was 0·88 (95% CI 0·79–0·98).

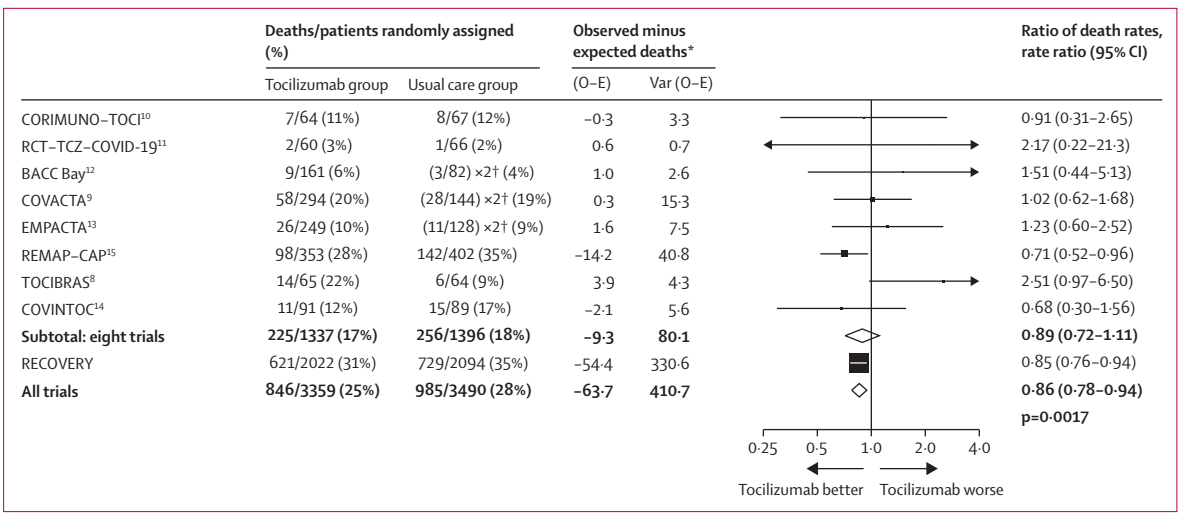

Figure 4: **Meta-analysis of mortality in randomised, controlled trials of tocilizumab in patients hospitalised with COVID-19**
O–E=observed–expected. Var=variance. *Log–rank O–E for RECOVERY, O–E from 2 × 2 contingency tables for the other trials. Rate ratio is calculated by taking ln rate ratio to be (O–E)/V with normal variance 1/V, where V=Var (O–E). Subtotals or totals of (O–E) and of V yield inverse-variance weighted averages of the ln rate ratio values. †For balance, controls in the 2:1 studies count twice in the control totals and subtotals, but do not count twice when calculating their O–E or V values. Heterogeneity between RECOVERY and eight previous trials combined, χ_1^2=0·2 (p=0·7).

amount of respiratory support at randomisation (figure 3). Given the number of hypothesis tests done, the suggestion of a larger proportional mortality reduction among those receiving a corticosteroid compared with those not (interaction p=0·01) might reflect the play of chance. An exploratory analysis showed that the effects of tocilizumab on 28-day mortality were similar for those randomly assigned ≤2 or >2 days since hospitalisation (interaction p=0·89). In eight previous trials of tocilizumab versus usual care, which included a total of 439 deaths among 2379 patients, allocation to tocilizumab was associated with a non-significant 11% reduction in mortality (rate ratio 0·89, 0·72–1·11; figure 4). After inclusion of the 28-day mortality results from RECOVERY into this meta-analysis, the mortality rate ratio from the nine trials was 0·86 (0·78–0·94), p=0·0017.

In prespecified subsidiary analyses, we found no significant effect of tocilizumab on subsequent receipt of non-invasive respiratory support or invasive mechanical ventilation among those on no respiratory support at randomisation (table 2, appendix p 50). Nor was there a significant effect on the rate of successful cessation of invasive mechanical ventilation among those on invasive mechanical ventilation at randomisation. However, allocation to tocilizumab reduced the use of haemodialysis or haemofiltration (6% vs 8%, risk ratio 0·72, 0·58–0·90, p=0·0046; table 2) among those not receiving haemodialysis or haemofiltration at randomisation. There was no evidence of excess deaths from non-COVID infections or other causes (appendix p 45). We observed no significant differences in the frequency of new cardiac arrhythmias (appendix p 46). There were three reports of serious adverse reactions believed to be related to tocilizumab: one each of otitis externa, *Staphylococcus aureus* bacteraemia, and lung abscess, all of which resolved with standard treatment.

Discussion

The results of this large, randomised trial indicate that tocilizumab is an effective treatment for hospitalised COVID-19 patients who have hypoxia and evidence of inflammation (CRP ≥75 mg/L). Treatment with tocilizumab improved survival and the chances of discharge from hospital by 28 days, and reduced the chances of progressing to require invasive mechanical ventilation. These benefits were consistent across all patient groups studied, including those receiving invasive mechanical ventilation, non-invasive respiratory support, or no respiratory support other than simple oxygen. The benefits of tocilizumab were clearly seen among those also receiving treatment with a systemic corticosteroid, which is now usual standard of care for COVID-19 patients requiring treatment with oxygen.[6,7]

Previous trials have provided some evidence that tocilizumab might shorten time to discharge or reduce progression to invasive mechanical ventilation or death.[9,13] Since mid-2020, eight randomised, controlled trials of tocilizumab for the treatment of COVID-19 have reported. These include seven small trials (fewer than 100 deaths in each) and the somewhat larger REMAP-CAP trial, which recruited critically ill patients with COVID-19, over 99% of whom required non-invasive respiratory support or invasive mechanical ventilation.[8–15] Taken together, these previous trials did not show a significant mortality benefit for treatment with tocilizumab (death rate ratio 0·89, 95% CI 0·72–1·11; figure 4). The RECOVERY trial contains around four times as much information as all the previous trials

combined. When all nine trials are considered together, allocation to tocilizumab is associated with a significant 14% proportional reduction in 28-day mortality. These results suggest that in COVID-19 patients who are hypoxic and have evidence of systematic inflammation, treatment with a combination of a systemic corticosteroid plus tocilizumab would be expected to reduce mortality by about one-third for patients receiving simple oxygen and nearly one-half for those receiving invasive mechanical ventilation.[6]

The RECOVERY results support the use of tocilizumab. Our results show that the benefits of tocilizumab extend to a broad group of patients receiving oxygen, with or without other forms of respiratory support, and that those benefits include a reduction in the need for invasive mechanical ventilation and renal replacement therapy. Since complicating bacterial infections are infrequent in the early hospitalisation period of COVID-19, this recognised concern in relation to the use of tocilizumab would be lessened with earlier use.[20] On the basis of the ISARIC4C database, approximately 49% of hospitalised COVID-19 patients in the UK would meet our inclusion criteria and hence would benefit from tocilizumab (ISARIC4C Investigators, personal communication). Sarilumab, an alternative IL-6 antagonist, is available but evidence of its efficacy is inconclusive[15,21,22] and the results of the largest trial (NCT04315298) are not yet published.

Strengths of this trial included that it was randomised, had a large sample size, and included patients requiring various amounts of respiratory support (from simple oxygen through to invasive mechanical ventilation) and has 99% completeness of follow-up for the primary outcome. CRP was chosen as the biomarker for inflammation in this study since it is widely used and affordable worldwide, it is correlated with serum IL-6 concentrations, and early clinical studies of COVID-19 had reported it to be associated with severity and prognosis, with a value of greater than 50 mg/L associated with severe disease and a concentration of around 75 mg/L distinguishing fatal from non-fatal cases.[23–28] Whether hypoxic patients with a CRP of less than 75 mg/L could benefit from tocilizumab is unknown. There are some limitations. We did not collect detailed information on non-COVID infections. Following random assignment, 16% of patients in the tocilizumab group reportedly did not receive this treatment and the reasons for this were not recorded. The size of the effects of tocilizumab reported in this paper are therefore an underestimate of the true effects of actually using the treatment. Hospital stay is very long for many of these patients and some outcomes beyond 28 days have not yet been captured. The preplanned analyses at 6 months will, however, provide additional information on the full effects of tocilizumab on clinical outcomes. Further work is also needed to consider the health economic benefits of tocilizumab and related IL-6 inhibitors in terms of both patient outcomes and usage of health-care resources (duration of hospital stay, and frequency of invasive mechanical ventilation and renal replacement therapy).

The RECOVERY trial has shown that for patients hospitalised with severe COVID-19, treatment with tocilizumab reduces mortality, increases the chances of successful hospital discharge, and reduces the chances of requiring invasive mechanical ventilation. These benefits are additional to those previously reported for dexamethasone. These findings require an update to clinical guidelines, which has already begun, and efforts to increase the global availability and affordability of tocilizumab.[29,30]

For more on **this policy** see https://www.ndph.ox.ac.uk/files/about/ndph-independence-of-research-policy-jun-20.pdf

For **trial details** see www.recoverytrial.net

For **policy and procedures** see https://www.ndph.ox.ac.uk/data-access

For the **form** see https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx

Contributors

This manuscript was initially drafted by PWH and MJL, further developed by the writing committee, and approved by all members of the trial steering committee. PWH and MJL vouch for the data and analyses, and for the fidelity of this report to the study protocol and data analysis plan. PWH, MM, JKB, LCC, SNF, TJ, KJ, WSL, AMo, AMu, KR, EJ, RH, and MJL designed the trial and study protocol. MM, MC, LP, G P-A, CB, RSa, KT, VJ, AA, RPT, DC, MS, RSt, BR, RH, the Data Linkage team at the RECOVERY Coordinating Centre, Health Records, and local clinical centre staff listed in the appendix collected the data. ES, NS, and JRE accessed and verified the data and did the statistical analysis. All authors contributed to data interpretation and critical review and revision of the manuscript. PWH and MJL had access to the study data and had final responsibility for the decision to submit for publication.

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Declaration of interests

The authors have no conflict of interest or financial relationships relevant to the submitted work to disclose. No form of payment was given to anyone to produce the manuscript. All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. The Nuffield Department of Population Health at the University of Oxford has a staff policy of not accepting honoraria or consultancy fees directly or indirectly from industry.

Data sharing

The protocol, consent form, statistical analysis plan, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, and other relevant study materials are available online. As described in the protocol, the trial steering committee will facilitate the use of the study data and approval will not be unreasonably withheld. De-identified participant data will be made available to bona fide researchers registered with an appropriate institution within 3 months of publication. However, the steering committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (eg, relating to data protection and privacy). The steering committee will have the right to review and comment on any draft manuscripts before publication. Data will be made available in line with the policy and procedures. Those wishing to request access should complete the form.

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