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Interleukin-6 blocking agents for treating COVID-19: a living systematic review (Review)

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[Intervention Review]

Interleukin-6 blocking agents for treating COVID-19: a living systematic review

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ABSTRACT

Background

Interleukin 6 (IL-6) blocking agents have been used for treating severe coronavirus disease 2019 (COVID-19). Their immunosuppressive effect might be valuable in patients with COVID-19 characterised by substantial immune system dysfunction by controlling inflammation and promoting disease tolerance.

Objectives

To assess the effect of IL-6 blocking agents compared to standard care alone or with placebo on efficacy and safety outcomes in COVID-19.

We will update this assessment regularly.

Search methods

We searched the World Health Organization (WHO) International Clinical Trials Registry Platform (up to 11 February 2021) and the L-OVE platform, and Cochrane COVID-19 Study Register to identify trials up to 26 February 2021.

Selection criteria

We included randomised controlled trials (RCTs) evaluating IL-6 blocking agents compared with standard care alone or with placebo for people with COVID-19, regardless of disease severity.

Data collection and analysis

We followed standard Cochrane methodology. The protocol was amended to reduce the number of outcomes considered. Two review authors independently collected data and assessed the risk of bias with the Cochrane Risk of Bias 2 tool. We rated the certainty of evidence with the GRADE approach for the critical outcomes such as clinical improvement (defined as hospital discharge or improvement on the scale used by trialists to evaluate clinical progression or recovery) (day (D) 28 / ≥ D60); WHO Clinical Progression Score of level 7 or above (i.e. the proportion of participants with mechanical ventilation +/- additional organ support OR death) (D28 / ≥ D60); all-cause mortality (D28 / ≥ D60); incidence of any adverse events; and incidence of serious adverse events.

Main results

We identified 10 RCTs with available data including one platform trial comparing tocilizumab and sarilumab with standard of care. These trials evaluated tocilizumab (nine RCTs including two platform trials; seven were reported as peer-reviewed articles, two as preprints; 6428 randomised participants); and two sarilumab (one platform trial reported as peer reviewed article, one reported as preprint, 880 randomised participants).

All trials included were multicentre trials. They were conducted in Brazil, China, France, Italy, UK, USA, and four were multi-country trials. The mean age range of participants ranged from 56 to 65 years; 4572 (66.3%) of trial participants were male. Disease severity ranged from mild to critical disease. The reported proportion of participants on oxygen at baseline but not intubated varied from 56% to 100% where reported. Five trials reported the inclusion of intubated patients at baseline.

We identified a further 20 registered RCTs of tocilizumab compared to placebo/standard care (five completed without available results, five terminated without available results, eight ongoing, two not recruiting); 11 RCTs of sarilumab (two completed without results, three terminated without available results, six ongoing); six RCTs of clazakisumab (five ongoing, one not recruiting); two RCTs of olokizumab (one completed, one not recruiting); one of siltuximab (ongoing) and one RCT of levilimab (completed without available results). Of note, three were cancelled (2 tocilizumab, 1 clazakisumab). One multiple-arm RCT evaluated both tocilizumab and sarilumab compared to standard of care, one three-arm RCT evaluated tocilizumab and siltuximab compared to standard of care and consequently they appear in each respective comparison.

Tocilizumab versus standard care alone or with placebo

a. *Effectiveness of tocilizumab for patients with COVID-19*

Tocilizumab probably results in little or no increase in the outcome of clinical improvement at D28 (RR 1.06, 95% CI 1.00 to 1.13; I^2 = 40.9%; 7 RCTs, 5585 participants; absolute effect: 31 more with clinical improvement per 1000 (from 0 fewer to 67 more); moderate-certainty evidence). However, we cannot exclude that some subgroups of patients could benefit from the treatment. We did not obtain data for longer-term follow-up (≥ D60).

The effect of tocilizumab on the proportion of participants with a WHO Clinical Progression Score of level of 7 or above is uncertain at D28 (RR 0.99, 95% CI 0.56 to 1.74; I^2 = 64.4%; 3 RCTs, 712 participants; low-certainty evidence). We did not obtain data for longer-term follow-up (≥ D60).

Tocilizumab reduces all-cause mortality at D28 compared to standard care alone or placebo (RR 0.89, 95% CI 0.82 to 0.97; I^2 = 0.0%; 8 RCTs, 6363 participants; absolute effect: 32 fewer deaths per 1000 (from 52 fewer to 9 fewer); high-certainty evidence). There is uncertainty around the effect on mortality at ≥ D60 (RR 0.86, 95% CI 0.53 to 1.40; I^2 = 0.0%; 2 RCTs, 519 participants; low-certainty evidence).

b. Safety of tocilizumab for patients with COVID-19

The evidence is very uncertain about the effect of tocilizumab on adverse events (RR 1.23, 95% CI 0.87 to 1.72; I^2 = 86.4%; 7 RCTs, 1534 participants; very low-certainty evidence). Nevertheless, tocilizumab probably results in slightly fewer serious adverse events than standard care alone or placebo (RR 0.89, 95% CI 0.75 to 1.06; I^2 = 0.0%; 8 RCTs, 2312 participants; moderate-certainty evidence).

Sarilumab versus standard care alone or with placebo

The evidence is uncertain about the effect of sarilumab on all-cause mortality at D28 (RR 0.77, 95% CI 0.43 to 1.36; 2 RCTs, 880 participants; low certainty), on all-cause mortality at ≥ D60 (RR 1.00, 95% CI 0.50 to 2.0; 1 RCT, 420 participants; low certainty), and serious adverse events (RR 1.17, 95% CI 0.77 to 1.77; 2 RCTs, 880 participants; low certainty). It is unlikely that sarilumab results in an important increase of adverse events (RR 1.05, 95% CI 0.88 to 1.25; 1 RCT, 420 participants; moderate certainty). However, an increase cannot be excluded

No data were available for other critical outcomes.

Authors' conclusions

On average, tocilizumab reduces all-cause mortality at D28 compared to standard care alone or placebo and probably results in slightly fewer serious adverse events than standard care alone or placebo. Nevertheless, tocilizumab probably results in little or no increase in the outcome clinical improvement (defined as hospital discharge or improvement measured by trialist-defined scales) at D28. The impact of tocilizumab on other outcomes is uncertain or very uncertain. With the data available, we were not able to explore heterogeneity. Individual patient data meta-analyses are needed to be able to identify which patients are more likely to benefit from this treatment.

Evidence for an effect of sarilumab is uncertain and evidence for other anti-IL6 agents is unavailable.

Thirty-nine RCTs of IL-6 blocking agents with no results are currently registered, of which nine are completed and seven trials were terminated with no results available. The findings of this review will be updated as new data are made available on the COVID-NMA platform (covid-nma.com).

PLAIN LANGUAGE SUMMARY

Can medicines that block interleukin-6 (a protein involved in immune responses) treat COVID-19?

Key messages

Treating COVID-19 with tocilizumab (a medicine that blocks interleukin-6) reduces the numbers of people who die within 28 days of treatment, and probably results in fewer serious unwanted effects than placebo treatment.

Studies of other medicines that block interleukin-6 to treat COVID-19 are under way. We will update this review when results from them become available.

COVID-19

COVID-19 is an infectious respiratory disease caused by a type of virus called a coronavirus. If the infection becomes severe, people may need intensive care and support in hospital, including machines to help them breathe (mechanical ventilation). Medicines that are currently used to treat other diseases are being tested in the search to find effective treatments for COVID-19.

Blocking interleukin-6

An immune response is how the body recognises and defends itself against harmful substances, such as viruses. COVID-19 can disrupt the immune system, causing it to over-react and produce dangerously high levels of inflammation. Interleukin-6 (IL-6) is a protein involved in triggering inflammation. Blocking the production of interleukin-6 could reduce inflammation and help the immune system to fight COVID-19.

Why we did this Cochrane Review

Tocilizumab and sarilumab are two medicines that block interleukin-6. They are used to treat other conditions that involve an "over-reactive" immune system, such as rheumatoid arthritis. We wanted to find out if medicines that block interleukin-6 can be used to treat COVID-19, and whether they might cause any unwanted effects.

What did we do?

We searched for studies that tested if medicines that block interleukin-6 could treat COVID-19.

We looked for randomised controlled studies, in which the treatments people received were decided by chance. This type of study usually gives the most reliable evidence about the effects of a treatment.

Search date: we searched for trials up to 26 February 2021.

What we found

We found 10 studies in 6896 people with COVID-19. The average age of people in the studies was 56 to 65 years, and 66% of the people enrolled were men. The studies took place in Brazil, China, France, Italy, the UK and the USA; four studies took place in more than one country. Three studies were funded by pharmaceutical companies.

The medicines tested were tocilizumab and sarilumab. Both medicines were compared against a placebo (a dummy treatment that appears identical to the medicine being tested but without any active medicine) or standard care. The results were measured 28 days after treatment and after 60 days or more.

We also found 41 more studies of medicines blocking interleukin-6 to treat COVID-19 that had not yet published any results. These included 20 studies of tocilizumab, 11 studies of sarilumab and 10 studies of other medicines. Some of those studies are still ongoing and we will update this review to include their results when published.

What are the main results of our review?

Compared with placebo treatment or standard treatment, treatment with tocilizumab:

· reduces the number of people who died, of any cause, after 28 days (evidence from 6363 people in 8 studies); on average, 32 fewer people per 1000 died when treated with tocilizumab plus standard care, compared with standard care alone or placebo.

· probably makes little or no difference to clinical improvement (which is defined as leaving hospital or improvement in COVID-19 symptoms) at 28 days (evidence from 5585 people in 7 studies).

· probably reduces slightly the number of serious unwanted effects, such as life-threatening conditions or death (evidence from 2312 people in 8 studies).

We are uncertain about the effects of tocilizumab treatment on:

- severity of COVID-19; that is, how many patients died of COVID-19 or needed a ventilator or additional organ support at 28 days (evidence from 712 people in 3 studies); or

- how many patients died, of any cause, after 60 days or more (evidence from 519 people in 2 studies).

No results were reported for tocilizumab after 60 days or more for improvement, or severity at 28 days of COVID-19.

We are uncertain about how sarilumab treatment affected the:

- numbers of people who died (of any cause) at 28 days (evidence from 880 people in 2 studies) and after 60 days (evidence from 420 people in 1 study); or

- the numbers of serious unwanted effects, such as life-threatening conditions or death (evidence from 880 people in 2 studies).

- Sarilumab probably does not cause more unwanted effects (of any type) than placebo treatment (evidence from 420 people in 1 study). No other results for sarilumab treatment were reported.

We were not able to explore which COVID-19 patients are more likely to benefit from this treatment.

Our confidence in our results

We are confident that tocilizumab reduced the number of deaths (from any cause) at 28 days. Our confidence in the other results for tocilizumab is moderate to low; further evidence may change our results. Our confidence in the results for sarilumab is low; further evidence is likely to change these results. Our confidence was lowered because some of the studies did not report all their results.

SUMMARY OF FINDINGS

Summary of findings 1. Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Patient or population: participants with mild/moderate/severe/critical COVID-19

Settings: Brazil, China, France, Italy, UK, USA

Intervention: tociliuzumab

Comparison: standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care/ placebo	Risk with tocilizumab				
Clinical improvement D28	**515 per 1000**	**545 per 1000** (515 to 581)	**RR 1.06** (1.00 to 1.13)	5585 (7 RCTs)	⊕⊕⊕⊖ **moderate** [1]	Data at D ≥ 60 was not available Clinical improvement was defined variably as an improvement from baseline in > 2 categories on a 7-category ordinal scale (2 studies); a decrease of at least 2 points on an ordinal clinical improvement scale (1 study); or hospital discharge or ready to discharge (7 studies)
WHO progression score (level 7 or above) D28	**262 per 1000**	**260 per 1000** (147 to 457)	**RR 0.99** (0.56 to 1.74)	712 (3 RCTs)	⊕⊕⊖⊖ **low** [2,3]	Data at D ≥ 60 was not available
All-cause mortality D28	**291 per 1000**	**259 per 1000** (239 to 283)	**RR 0.89** (0.82 to 0.97)	6363 (8 RCTs	⊕⊕⊕⊕ **high** [4]	
All-cause mortality D60	**133 per 1000**	**114 per 1000** (70 to 186)	**RR 0.86** (0.53 to 1.40)	519 (2 RCTs)	⊕⊕⊖⊖ **low** [5,6]	
Adverse events	**457 per 1000**	**562 per 1000**	**RR 1.23**	1534	⊕⊖⊖⊖	

		(397 to 786)	(0.87 to 1.72)	(7 RCTs)	**very low** [7,8,9]
Serious adverse events	**149 per 1000**	**132 per 1000** (111 to 157)	**RR 0.89** (0.75 to 1.06)	2312 (8 RCTs)	⊕⊕⊕⊖ **moderate** [7]
Time to clinical improvement 28 to 90 days follow-up	**High**		**HR 1.23** (1.08 to 1.39)	2118 (6 RCTs)	⊕⊕⊕⊖ **moderate** [1, 13]
	889 per 1000	**933 per 1000** (917 to 957			
Time to WHO progression score (level 7 and above) 28 to 90 days follow-up	**Low**		**HR 0.62** (0.42 to 0.91)	762 (3 RCTs)	⊕⊕⊕⊖ **moderate** [10, 11, 13]
	123 per 1000	**78 per 1000** (54 to 113)			
Time to death follow-up 28 to 90 days	**Low**		**HR 0.65** (0.51 to 0.83)	1152 (3 RCTs)	⊕⊕⊖⊖ **low** [2, 12, 13]
	37 per 1000	**24 per 1000** (19 to 31)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio; **HR**: Hazard Ratio: **WHO**: World Health Organization

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Risk of bias downgraded by 1 level: some concerns due to deviation from intended interventions and outcome measurement
[2] Risk of bias downgraded by 1 level: some concerns due to deviations from intended interventions
[3] Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm
[4] Despite some concerns due to deviation from intended interventions, risk of bias was not downgraded because the studies at risk contributed < 20% weight to the effect estimate.
[5] Despite some concerns due to deviation from intended intervention in 1 study, risk of bias was not downgraded because this study contributed only 30% weight to the effect estimate.

[6] Imprecision downgraded by 2 levels: due to low number of events and a wide confidence interval consistent with the possibility for benefit and the possibility for harm
[7] Risk of bias downgraded by 1 level: some concerns regarding randomisation, deviations from intended interventions, outcome measurement and selection of reported result
[8] Inconsistency downgraded by 1 level: I^2 = 86.4%
[9] Imprecision downgraded by 1 level: due to a wide confidence interval consistent with the possibility for no effect and the possibility for harm
[10] Despite some concerns due to deviation from intended intervention in 2 studies, risk of bias was not downgraded.
[11] Imprecision downgraded by 1 level: due to low number of events and a wide confidence interval consistent with the possibility for benefit and the possibility for little or no effect
[12] Imprecision downgraded by 1 level: due to low number of events and participants
[13] Control group risk at 28 days from Stone 2020

Summary of findings 2. Sarilumab compared to standard care for severe/critical COVID-19

Sarilumab compared to standard care for severe/critical COVID-19

Patient or population: participants with severe/critical COVID-19

Settings: Brazil, China, France, Italy, UK, USA

Intervention: sarilumab

Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Clinical improvement D28	-	-	-	-	-	Outcome of interest not reported
WHO progression score (level 7 or above) D28	-	-	-	-	-	Outcome of interest not reported
All-cause mortality D28	**299 per 1000**	**230 per 1000** (129 to 407)	**RR 0.77** (0.43 to 1.36)	880 (2 RCTs)	⊕⊕⊖⊖ **low** [1,2]	
All-cause mortality D60 or above	**105 per 1000**	**105 per 1000** (52 to 209)	**RR 1.0** (0.5 to 2.0)	420 (1 RCT)	⊕⊕⊖⊖ **low** [2, 3]	
Adverse events	**640 per 1000**	**672 per 1000** (563 to 799)	**RR 1.05** (0.88 to 1.25)	420 (1 RCT)	⊕⊕⊕⊖ **moderate** [4,5]	
Serious adverse events	**62 per 1000**	**73 per 1000**	**RR 1.17**	880	⊕⊕⊖⊖	

		(48 to 110)	(0.77 to 1.77)	(2 RCTs)	**low** [2,4]	
Time to clinical improvement follow-up 90 days	**Moderate**		**HR 1.28** (0.88 to 1.87)	880 (2 RCTs)	⊕⊕⊖⊖ **low** [6,7,9]	Clinical improvement defined as hospital discharge
	460 per 1000	**546 per 1000** (419 to 684)				
Time to WHO progression score (level 7 and above)	-	-	-	-	-	Outcome of interest not reported
Time to death follow-up 90 days	**Moderate**		**HR 0.55** (0.33 to 0.91)	460 (1 RCT)	⊕⊕⊖⊖ **low** [1, 5,8,9]	
	330 per 1.000	**198 per 1000** (124 to 305)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio; **HR**: Hazard Ratio, **WHO**:World Health Organization

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Despite some concerns due to deviation from intended interventions, we did not downgrade for risk of bias
[2] Imprecision downgraded by 2 levels: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and few events
[3] Despite some concerns due to selection of the reported result, we did not downgrade for risk of bias
[4] We presume that the adverse event rates and the corresponding relative risks, are similar across diverse settings; therefore not downgraded for indirectness.
[5] Imprecision downgraded by 1 level: few events
[6] Risk of bias downgraded by 1 level: some concerns due to deviations from intended intervention and outcome measurement
[7] Imprecision downgraded by 1 level: wide confidence interval consistent with the possibility for benefit and the possibility for no effect
[8] Indirectness downgraded by 1 level: single multicentre study only from high-income countries, therefore results in this population might not be generalisable to other settings
[9] Control group risk taken from Gordon REMAP-CAP 2021 at 30 days

BACKGROUND

Description of the condition

In December 2019, a novel coronavirus outbreak began in Wuhan, Hubei Province, China. Infection with this severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly. The World Health Organization (WHO) declared the coronavirus 19 (COVID-19) disease a pandemic on 11 March 2020 (WHO 2020a). The COVID-19 prevalence has increased exponentially in almost all countries during the first and subsequent waves (Worldometer 2020). The clinical spectrum of SARS-CoV-2 pneumonia ranges from mild to severe and critical manifestations. Approximately 15% of patients with SARS-CoV-2 infection develop severe COVID-19 pneumonia (Guan 2020). Enormous efforts are focused on finding treatments to reduce the need of invasive mechanical ventilation and/or the risk of death in these patients.

Some authors have proposed that patients at high risk of COVID-19 may experience a "cytokine storm"; a complex milieu of immune mis-firing characterised by an early interferonopathy followed by hypercytokinaemia with high inflammatory markers and low reparative growth factors (Bastard 2020; Galani 2020; Lucus 2020; Mehta 2020; Pedersen 2020). In this milieu, Interleukin 6 (IL-6) stands out as a particularly important biomarker (Chen 2020; Herold 2020; Laguna-Goya 2020; Stukas 2020). IL-6 levels or C-reactive protein (CRP), a marker of IL-6 driven inflammation, are associated with the severity of the disease (Caricchio 2020; Galvan-Roman 2021; Knight 2020; Manson 2020; Webb 2020).

Description of the intervention

IL-6 blocking agents are a class of therapeutic agents directed against the IL-6 peptide or receptor. Available IL-6 blocking agents are classified as anti-IL-6 receptor monoclonal antibodies (e.g. sarilumab, tocilizumab, levilimab) or anti-IL-6 monoclonal antibodies (siltuximab, olokizumab, clazakizumab).

How the intervention might work

IL-6 blockers are beneficial in some hyperinflammatory diseases, such as rheumatoid arthritis (Scott 2017), giant cell arteritis (Stone 2017), and cytokine release syndrome induced by chimeric antigen receptor T-cell therapy (Kotch 2019). SARS-CoV-2 infection induces a dose- and time-dependent production of cytokines, including IL-6 (Kang 2020).

The immunosuppressive effect of IL-6 blockers might be valuable in patients with COVID-19 who are characterised by substantial immune system dysfunction by controlling inflammation and promoting disease tolerance (Campochiaro 2020).

Why it is important to do this review

Given the urgent need for an effective treatment for COVID-19 globally, patients have been treated with several costly immune-modulating compounds including JAK (Janus kinase) inhibitors (Cao 2020; Kalil 2021), and specific cytokine blockers (Guaraldi 2020). The main immunomodulatory therapies that have been explored are JAK inhibition (broad suppression of inflammatory cytokines) and targeted inhibition of IL-1 and IL-6 (CORIMUNO-19 Collaborative group 2021). Policymakers, scientific experts and the public need high-quality, up-to-date evidence evaluating the effectiveness and safety of IL-6 blocking agents for treating COVID-19. This is a high-priority question, for which the existing evidence is inconclusive (Solis-García Del Pozo 2020). A living systematic review is an optimal approach to track and assess the effectiveness of IL-6 blocking agents use in patients with COVID-19.

This evidence synthesis will be updated weekly on the COVID-NMA platform (covid-nma.com). This published Cochrane Review will be updated when new evidence emerges with potential to change the certainty of the evidence or the review authors' conclusions, or at least every six months if new evidence is available. The process of the living systematic review is described in Appendix 1.

OBJECTIVES

To assess the effects of IL-6 blocking agents compared with standard care alone or with placebo on effectiveness and safety outcomes in patients with COVID-19.

This review is part of a larger project: the COVID-NMA project (Boutron 2020a). The COVID-NMA project provides decision-makers with a complete, high-quality and up-to-date mapping and synthesis of evidence on interventions for preventing and treating COVID-19. We developed a master protocol on the effect of all interventions for preventing and treating COVID-19 (Boutron 2020b). Our results are made available and updated weekly on the COVID-NMA platform at covid-nma.com.

This living review focuses on SARS-CoV-2 and does not consider studies evaluating treatment with IL-6 blocking agents for other coronavirus infections affecting humans.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of any design with no restrictions on language. The following trial designs were eligible for inclusion: parallel group, cluster, cross-over and factorial. Early-phase clinical trials, single-arm trials, non-randomised studies and modeling studies of interventions for COVID-19 were excluded as were prognosis studies, systematic reviews and meta-analyses, and diagnostic test accuracy studies.

The protocol of this review is available on PROSPERO (CRD42020214700).

Types of participants

We included trials evaluating children or adults with suspected, probable or confirmed ambulatory or hospitalised COVID-19 (see classification in Appendix 2; (WHO 2020b)).

Types of interventions

We included the following IL-6 blocking agents with no restriction on dose, frequency, or mode of administration.

1. Tocilizumab (humanised monoclonal antibody against the IL-6 receptor)
2. Sarilumab (human monoclonal antibody against the IL-6 receptor)
3. Clazakizumab (humanised rabbit monoclonal antibody against IL-6)

4. Olokizumab (humanised monoclonal antibody against IL-6)
5. Siltuximab (chimeric monoclonal antibody against IL-6)
6. Levilimab (human monoclonal antibody against the IL-6 receptor)

Comparator(s)

We considered the following types of comparators in this review.

1. Standard care alone or with placebo.
2. Standard of care as defined by trialists.

Types of outcome measures

Our outcome selection was based on the CORE outcome sets developed by the WHO (WHO Working Group 2020), and advice from content experts.

We predefined the following critical and important outcome measures.

Critical outcomes

The following outcomes with related time points reported as days (D) of follow-up were considered:

1. clinical improvement (D28 / ≥ D60) defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery. We recorded the scale and the threshold used by authors to define improvement as appropriate;
2. WHO Clinical Progression Score of level 7 or above (i.e. mechanical ventilation +/- additional organ support (extra corporeal membrane oxygenation (ECMO), vasopressors or dialysis) OR death (D28 / ≥ D60);
3. all-cause mortality (D28 / ≥ D60);

We reported all assessments performed at D60 and later under ≥ D60

Safety outcomes

1. Incidence of any adverse events (AEs)
2. Incidence of serious AEs (SAEs)

For each time point, we considered time of randomization as D0. However, if not reported, we considered D0 as reported by the authors.

When outcomes are assessed at time points other than those selected by the review, we chose the closest (e.g. D15 for D28).

Important outcomes

1. Time to clinical improvement
2. Time to WHO Clinical Progression Score of level 7 or above
3. Time to death

We present all critical and important outcomes in Summary of findings 1; Summary of findings 2.

Search methods for identification of studies

The search relies on the search for the COVID-NMA initiative (Boutron 2020a; Boutron 2020b)

The initial search strategy was developed with an information specialist from the Cochrane Editorial & Methods Department (Robin Featherstone).

We conducted an evaluation of two secondary sources the L-OVE platform and the Cochrane COVID-19 Study Register. We found that searching both secondary sources allowed identifying 100% of the reports of RCTs (preprint or peer-reviewed publication) assessing treatment or preventive interventions for COVID-19 (see Appendix 3). We updated our search 7 September 2020, and now only search the L-OVE platform, the Cochrane COVID-19 Study Register, the Retraction Watch Database and all other resources listed below. The last search date was 26 February 2021.

Electronic searches

We searched the following databases.

1. The **L-OVE platform** (https://app.iloveevidence.com/covid19), every working day since 7 September 2020 (last search February 26, 2021).
2. The **Cochrane COVID-19 Study Register** (https://covid-19.cochrane.org/), every working day since 7 September 2020 (last search February 26, 2021).
3. · **PubMed** every working day up to 7 September 2020.
4. **MedRχiv** (https://www.medrxiv.org). This is a free online archive and distribution server for complete but unpublished manuscripts (preprints) in the medical, clinical, and related health sciences. A curated list of records for COVID-19 and SARS-CoV-2 is available at https://connect.biorxiv.org/relate/content/181. Note that this list also includes sources listed in bioRχiv, but we only screened the sources published on MedRχiv. We searched this archive every working day from 1 March 2020 to 7 September 2020.
5. **CNKI** (China National Knowledge infrastructure, https://www.cnki.net/), database and (http://journal.yiigle.com/). We searched on 17 April 2020.
6. **Chinaχiv** http://chinaxiv.org/. This is a free online archive and distribution server for complete but unpublished manuscripts (preprints) in Chinese. We searched every working day from 1 March 2020 to 7 September 2020.
7. **LitCOVID** (https://www.ncbi.nlm.nih.gov/research/coronavirus/), is a curated database that tracks scientific evidence on COVID-19 published in PubMed. The hub is updated daily and studies are categorised by domain (e.g. “transmission” or “treatment” (https://www.nature.com/articles/d41586-020-00694-1). We screened studies listed under “treatment” from 1 March 2020 to 1 June 2020. We decided to stop searching LitCOVID because it did not identify any trials that were not already identified in the primary source.
8. **WHO database of publications on coronavirus disease** (COVID-19) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov), from 1 March 2020 to 28 August 2020. We decided to stop searching these secondary sources because they did not identify any trials that were not already identified in the primary source.

We screened other sources such as the **EPPI-Centre living map of evidence** (http://eppi.ioe.ac.uk/COVID19_MAP/COVID_map_v5.html), and **Meta-evidence**, developed by Campbell UK & Ireland (http://meta-evidence.co.uk/), from 1 March 2020 to 28 August 2020. We decided to stop searching these

secondary sources because they did not identify any trials that were not already identified in the primary source.

We also searched the **Retraction Watch Database** for retracted trials (https://retractionwatch.com/retracted-coronavirus-covid-19-papers/), (26 February 2021).

If no peer-review publication was available, we extracted data from the preprint. We recognise that preprints are not peer reviewed and are living documents that can be updated or published. We developed a preprint tracker in collaboration with a research team from the French National Centre for Scientific Research, which systematically informs us when a preprint is updated or published. As soon as an update was identified, we checked the data for discrepancies against that already extracted and recorded the data not available in the initial report and updated the analysis if needed.

Searching other resources

We searched the following trial registries for unpublished and ongoing trials:

1. the **WHO International Clinical Trials Registry Platform (ICTRP**, https://www.who.int/ictrp/en/), to identify ongoing and completed clinical trials on COVID-19. We used the *List By Health Topic*: 2019-nCoV / COVID-19 filter and retrieved all studies identified. (search 11 February 2021);
2. we intended to search the **European Medicines Agency (EMA) clinical data website** (https://clinicaldata.ema.europa.eu/web/cdp/home), to identify trials submitted to the EMA and searched for the Clinical Study Report of eligible trials (search 26 February 2021). However, the website was not accessible. There is currently some discussion between various stakeholders and the EMA to request for publication of clinical reports of COVID-19 interventions.
3. we also searched the **US Food and Drug Administration (FDA) website** to identify FDA approval trials (https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19), (search 26 February 2021).

Data collection and analysis

As part of the COVID-NMA living systematic review (Boutron 2020b), we search, screen, and extract data daily. An updated synthesis is reported online at least weekly.

Selection of studies

Two review authors screened all retrieved titles and abstracts for eligibility; all excluded abstracts were screened in duplicate. Two review authors independently screened full-texts of reports. We resolved discrepancies on exclusion and screening of full texts by consensus between both reviewers or by involving a third reviewer. We recorded reasons for exclusion for all studies excluded after full-text review.

We use an Excel spreadsheet to document search dates and numbers of citations identified. The screening of records and abstracts was done in duplicate independently using Rayyan (Ouzzani 2016). We resolved discrepancies any disagreements by involving a third reviewer .

Data extraction and management

Two review authors independently read each preprint, peer-reviewed publication, protocol, or other study reports, evaluated the completeness of the data availability, and assessed the risk of bias. We used a specific structured online data extraction form. All discrepancies automatically identified by the online tool were discussed by both review authors involved in the data extraction to reach consensus.

The information we extracted included study characteristics (such as first author, publication year and journal, funding source), number of participants randomised, patient characteristics (e.g. severity of clinical presentation), comorbidities, cointerventions, intervention details (e.g. dose, schedule), outcome measures, and 'Risk of bias' assessment.

We systematically contacted the trial authors to ask them for supplementary information unavailable from the trial reports. These data were requested by a personalised email sent by the WHO as a partner in the COVID-NMA project.

Disease severity was classified as described below according to the clinical status or clinical management of patients. This classification relies on existing classification and clinical expertise (WHO 2020c; WHO 2020b). We considered the description of eligibility criteria as well as the baseline characteristics of participants and classified the severity as follows:

1. **mild disease ambulatory:** "outpatients" whose clinical symptoms are mild with no sign of pneumonia on imaging;
2. **mild disease:** clinical symptoms requiring hospitalization but no need for supplemental oxygen;
3. **moderate disease:** fever and respiratory symptoms with radiological findings of pneumonia and requiring standard oxygen therapy O_2 (3 to 5 L/min);
4. **severe disease:** meeting any of the following criteria:
   a. respiratory distress ($\geqq$ 30 breaths/min);
   b. oxygen saturation $\leq$ 93% at rest in ambient air or oxygen saturation $\leq$ 97% with $O_2 \geq$ 5 L/min;
   c. $PaO_2/FiO_2 \leqq$ 300 mmHg (1 mmHg = 0.133 kPa). PaO_2/FiO_2 in high-altitude areas (> 1000 metres above sea level) is corrected by the following formula: PaO_2/FiO_2 x (atmospheric pressure (mmHg)/760);
   d. patients hospitalised on non-invasive ventilation (NIV)/high flow nasal oxygen (HFNO);
5. **critical disease: cases meeting the following criteria:**
   a. respiratory failure requiring invasive mechanical ventilation without or with vasopressor, dialysis, or extracorporeal membrane oxygenation (ECMO).

It is worth mentioning that since the classification of severity class was heterogenous among studies, we reclassified the participant disease severity based on the above severity criteria. Consequently, the severity reported by investigators might differ from the severity reported in this review. For example, Gordon REMAP-CAP 2021 classified the included participants as critical, yet according to our definition we classified them as severe-critical (patients who receive non-invasive ventilation or high flow nasal cannula are considered as severe according to the classification detailed above).

When no data related to these classifications were available, we requested the information from authors.

Assessment of risk of bias in included studies

We assessed the trials using the Cochrane Risk of Bias 2 (RoB 2) tool for RCTs (Sterne 2019).

The Cochrane RoB 2 tool is structured into five domains:

1. risk of bias arising from the randomization process;
2. risk of bias due to deviations from intended interventions;
3. risk of bias due to missing outcome data;
4. risk of bias in measurement of the outcome;
5. risk of bias in the selection of the reported result.

A series of "signalling questions" elicit information relevant to 'Risk of bias' assessment within each domain. The response options to the signalling questions are: "yes"; "probably yes"; "probably no"; "no"; and "no information". A 'Risk of bias' judgement for each domain is generated by an algorithm, based on answers to the signalling questions. Judgement can be "low", "some concerns" or "high" risk of bias. Overall risk of bias is considered "low" if all domains are at "low risk"; "some concerns" if at least one domain has "some concern" and no domain at "high" risk of bias; and "high" if at least one domain is at "high risk".

We assessed the risk of bias for all critical and important outcomes listed in the protocol of the living systematic review COVID-NMA (Boutron 2020b).

In the context of this review, we are interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions were received as intended (the Intention-to-treat (ITT) effect).

The Cochrane Bias Methods Group developed a training material on 'Risk of bias' assessment tool RoB2, which is used by the systematic reviewers participating in data extraction and 'Risk of bias' assessment for the COVID-NMA platform (available upon request).

We recorded judgements for each domain and time point by using an online data extraction tool.

Two review authors independently assessed the risk of bias of each study. All 'Risk of bias' assessments were done at the outcome level by two independent review authors with consensus in case of disagreement. Review authors had epidemiological training or were members of the Cochrane Response team. They were trained using the material developed by the Cochrane Bias Methods Group. Each review author independently assessed the included manuscripts and used signalling questions for each domain of bias, which was fed into the related algorithm to obtain a judgement. Both review authors recorded their judgement and support for judgement. However, answers to signalling questions were not recorded. For the consensus, all disagreements in judgement were identified, discussed until consensus was achieved. If needed, a third review author was involved.

To ensure standardisation of judgement and justification, the review authors as well as the COVID-NMA core team revised the assessments/support for judgement.

In the context of the COVID-19 pandemic, we also standardized our assessment of some domains.

Domain 2. Risk of bias due to deviations from intended interventions.

In trials where participants and carers were not blinded, we specified some deviations that could arise because of the trial context and could affect the trial outcomes.

A. Cross-over from the control group to the intervention group

When the number of patients in the control receiving the intervention was important, this domain was rated as 'some concern'.

When the cross-over was planned in the protocol for participants with clinical worsening, we decided to rate this domain as 'some concern' because the decision to provide the treatment could have been influenced by the trial context.

B. Cointerventions

The following cointerventions could affect the trial outcomes:

1. remdesivir and other antivirals;
2. corticosteroids;
3. biologics.

When these cointerventions were reported and balanced, this domain was assessed as 'low' risk of bias. When these cointerventions were reported but imbalanced, this domain was rated as 'some concern' and not 'high risk' of bias as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.

Domain 2. Analysis to estimate the effect of assignment

Intention-to-treat analyses were considered appropriate.

When the analysis was not an ITT analysis the rating of this domain was made on a case-by-case basis according to:

1. the number of participants who crossed over and were not analyzed in the group allocated;
2. the number of participants excluded from the analysis for reason other than missing data as well as imbalance between arms in terms of number and reasons for exclusion.

Of note, for critical outcomes (i.e. binary outcomes), the analysis evaluated was usually based on our analysis where we considered all participants randomised as the denominator.

Domain 4. Risk of bias in measurement of the outcome

We prespecified the following rules.

1. Clinical Improvement (D28/ ≥ D60/time to event): assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.
2. WHO clinical progression score level 7 or above (D28/ ≥ D60/time to event): assessment of this outcome is probably not influenced by knowledge of the intervention assignment.

3. All-cause mortality (D28/ ≥ D60/time to event): assessment of this outcome is not influenced by knowledge of the intervention assignment.
4. Adverse events and serious adverse event:
   a. when detection of events relies only on measures that cannot be influenced by judgement (e.g., laboratory detected events): assessment of this outcome is probably not influenced by knowledge of the intervention assignment;
   b. when detection events rely only on measures that can be influenced by judgement (e.g., clinically and laboratory detected events): assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.

Measures of treatment effect

For dichotomous outcomes, we calculated the relative risk (RR) with 95% confidence intervals (CIs) as a measure of effect. We extracted the number of events and number of total participants in each trial arm. For time-to-event outcomes, we extracted the hazard ratio (HR) with 95% CIs. When these were not provided, we attempted to obtain them using the tools provided in Tierney 2007. When confidence intervals were not reported, but credible intervals were reported instead, we extracted the latter. In the absence of prior information these two are not expected to differ substantially numerically. For time to improvement, when available, we extracted the data with death treated as a competing risk. When several analyses were reported, we extracted results obtained from the ITT analysis whenever these were available. If ITT results were not available, results from any modified ITT analyses were extracted.

Unit of analysis issues

We treated comparisons from multi-arm or platform trials as independent two-arm trials since we did not pool comparisons of different drugs in the same meta-analysis. We did not identify any cross-over or cluster-randomized trials. If we do identify eligible cluster-randomized trials in future updates of the review, we will extract results that properly account for the cluster design (such as based on a multilevel model or on generalized estimating equations). If such an analysis is not reported, we will try to obtain an estimate of the intraclass correlation coefficient and calculate data required for the meta analyses, taking the design effect into consideration.

Dealing with missing data

For missing outcome data, we extracted the number of participants who dropped out before completing the trial and how trial authors handled missing outcome data. In our primary analysis for the critical outcomes, we followed a conservative approach assuming that participants with missing outcome data did not experience the event of interest. Hence, we calculated all RRs with the number of participants randomised in each group in the denominator. We also conducted sensitivity analyses to assess the potential impact of missing outcome data on the results by using an available-case analysis with the number of participants analyzed (e.g. only participants without missing outcome data or only patients who received treatment) in the denominator (see Sensitivity analysis section).

Assessment of heterogeneity

We generated descriptive statistics for both the trial and population characteristics and examined the distribution of important clinical and methodological variables (e.g. age, disease severity, pre-existing conditions and comorbidities, location). We used visual inspection of forest plots, the I^2 statistic and the magnitude of between-study variance (τ^2) to estimate the level of heterogeneity. We did not conduct prediction intervals (the interval within which the effect of a future trial is expected to lie (Riley 2011)), and comparison of with appropriate empirical distributions (Turner 2012), in this review because of the small number of trials; however, these are planned for future updates if appropriate

Assessment of reporting biases

Assessing risk of bias due to missing results in the synthesis

We assessed the risk of bias due to missing results in the synthesis according to the framework proposed in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

We used searches in trial registries to identify any initiated, ongoing, or completed, but not published trials meeting this review's eligibility criteria. We contacted all responsible parties to obtain an updated report of the results included in the trial registry. For published trials, we contacted the corresponding authors to obtain the missing data.

We checked whether the results of all our critical and important outcomes were reported as prespecified in the trial register. When registration was not prospective, we also checked the protocol or statistical analysis plan if available.

When any trial results were not available, we used a matrix indicating availability of study results as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020), and Kirkham 2018.

We checked whether results were unavailable because of the P value, magnitude, or direction of the result. We considered risk of bias due to missing results if one specified outcome of the registry was lacking in the main report because of these reasons.

Due to the small number of trials, we could not assess the potential for reporting bias across studies graphically or statistically.

Data synthesis

We have combined trials evaluating the same drug with standard care alone or with placebo comparators together under the same comparison. We included all eligible RCTs in the primary analysis, regardless of the 'Risk of bias' assessment.

For binary outcomes, we calculated the logRRs and their standard error using the number of events and the number of total participants in each arm. Then we pooled the trial-specific effect sizes. For time-to-event outcomes, we directly extracted the HRs and the respective 95% CIs from the trial reports and subsequently these were pooled in the meta-analysis.

For each direct comparison with at least two trials providing data, we presented effect estimates with 95% CIs. We used the random-effects model to incorporate the anticipated clinical and methodological heterogeneity across trials. We treated

comparisons from multi-arm or platform trials as independent two-arm trials since we did not pool comparisons of different drugs in the same meta-analysis.

All analyses were conducted using our R-shiny application (available from https://covid-nma.com/pairwise_meta_analysis/), which is based on the metafor package in R.

Subgroup analysis and investigation of heterogeneity

We carried out pre-specified subgroup analyses to explore the impact of trial location (single countries versus multinational). Post-hoc subgroup analyses included funding sources (private versus public/non-profit versus mixed) and conflict of interests (conflict of interests declared versus no conflict of interests).

Sensitivity analysis

We performed sensitivity analyses by excluding trials with high overall risk of bias and RCTs reported as preprint only. In order to assess the potential impact of missing outcome data on the results by using an available-case analysis with the number of participants analyzed, we also ran the analyses by using the number of participants analyzed, instead of those randomised, (Chaimani 2018; Mavridis 2015; Mavridis 2018; White 2008). A post-hoc sensitivity analysis was carried out to check the robustness of results after excluding trials that involved participants with all types of severity.

Summary of findings and assessment of the certainty of the evidence

To evaluate the confidence in the results of the pairwise comparisons for critical and important outcomes, we used the GRADE approach (Schünemann 2019). We prepared two 'Summary of findings' tables to present estimated relative and absolute risks. Overall certainty of the evidence for each outcome was assessed by one review author and cross-checked by another review author using the GRADE classification (GRADEpro GDT).

RESULTS

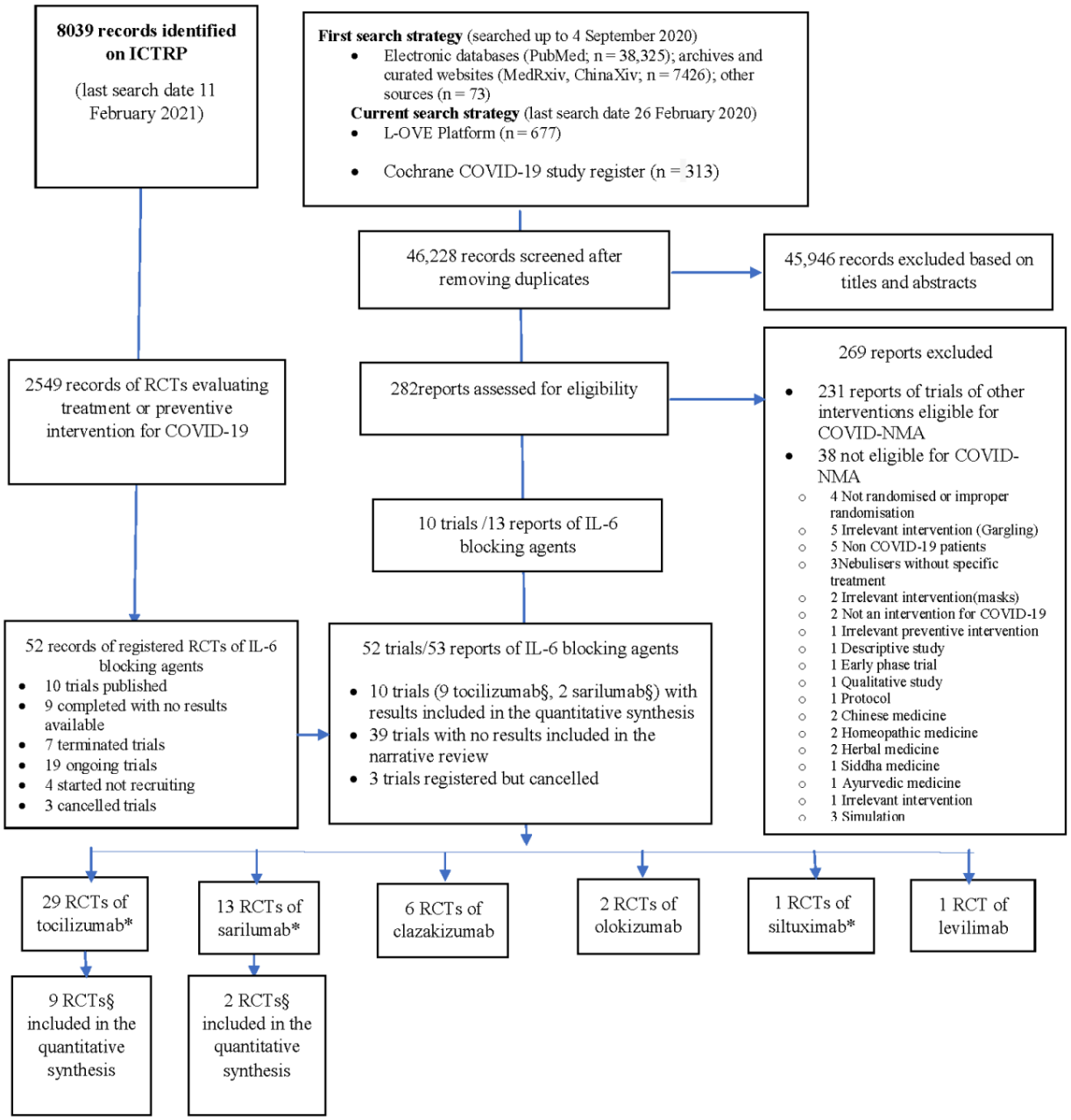
Description of studies

For a full description of studies please see the Characteristics of included studies; Characteristics of excluded studies; and the Characteristics of registered studies in Appendix 4.

Results of the search

The results of our searches are detailed in Figure 1. On 26 February 2021, we retrieved a total of 46,814 references by searching electronic bibliographic databases. After excluding duplicates, we screened 46,228 records: 282 were eligible for full-text screening. Key excluded studies are listed in Characteristics of excluded studies. Ten RCTs (seven published in peer-reviewed journals and three reported as preprints) evaluating IL-6 blocking agents were included in this review. Nine RCTs evaluated tocilizumab including one platform trial evaluating tocilizumab and sarilumab, and one three-arm trial evaluated sarilumab.

Figure 1. Flowchart of included RCTs of interleukin 6 (IL-6) blocking agents (last search date 11 February 2021). COVID-NMA is a living systematic review of all trials assessing treatment and preventive interventions for COVID-19 (Boutron 2020b). This review is a sub-review of COVID-NMA. *two multiple-arm RCTs evaluated both tocilizumab and sarilumab, one three-arm RCT evaluated tocilizumab and siltuximab and consequently they appear twice. §one multi-arm RCT evaluated both tocilizumab and sarilumab



We did not identify any retracted articles. The search of the US Food and Drug Administration website did not retrieve any reports. The search in ICTRP identified 39 registered trials with no results available and three cancelled registered trials (two evaluating tocilizumab and one clazakizumab).

We also contacted the named contacts for trials registered with no associated publication of results. The responses are detailed in Appendix 5 and Appendix 6 . We did not classify any trial as awaiting classification.

Overall, considering the data available in trial registries and the answers obtained from responsible parties, we identified 29 RCTs

of tocilizumab (seven published in peer-reviewed journals, two reported as preprints, five completed with no results available, five terminated with no results available, eight ongoing, two not recruiting); 13 RCTs of sarilumab (one published in peer-reviewed journal, one published as preprint, two completed with no results available, three terminated with no results available, six ongoing); six RCTs of clazakisumab (five ongoing, one not recruiting); two RCTs of olokizumab (one completed with no results available, one not recruiting); one of siltuximab (ongoing); one RCT of levilimab (completed with no results available). Of note, two RCTs were multiple arm/platform trials evaluating both tocilizumab and sarilumab compared to standard of care (one published in a peer-reviewed journal, one terminated with no results available), one three-arm RCT evaluating tocilizumab and siltuximab compared to standard of care and consequently they appear in each respective comparison

Included studies

See: Characteristics of included studies

Source of the data

Reports of the 10 RCTs with results were published in peer-reviewed journals (n = 7) (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021), or available as preprints (n = 3) (Horby RECOVERY 2021; Lescure 2021; Wang 2020). No results were posted on clinical trial registries. We contacted corresponding authors of nine trials to request for additional data; three provided information (Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020), and one agreed to provide data when the trial is published in a peer-reviewed journal (Wang 2020. No answers were obtained from the rest of the trial authors. One included study was only recently published we have not yet contacted the authors (Horby RECOVERY 2021).

Study design

Eight trials used a two-arm parallel-group randomised design and three were platform trials/multiple arms, and one evaluated tocilizumab and sarilumab. Four were placebo-controlled trials (Lescure 2021; Rosas COVACTA 2021; Salama EMPACTA 2020; Stone 2020). The median sample size was 315.5 participants (interquartile range (IQR): 128.25 to 545.5) (range 65 to 4116). Four trials did not achieve their target sample size; Salvarani 2020 achieved 32% (126/398) of the target population and the trial Scientific Committee decided to interrupt the trial for futility; Wang 2020 achieved only 35% (65 randomised/188 planned) of the sample size because of the rapid decline in the numbers of patients with COVID-19 in China; Gordon REMAP-CAP 2021 was stopped at a scheduled interim analysis following the decision of the Data Safety Monitoring Board; Veiga TOCIBRAS 2021 was terminated after the first interim analysis following the recommendations of the data monitoring committee, owing to an excess number of deaths at 15 days in the tocilizumab group. Further, results from Horby RECOVERY 2021 are results of a preliminary analysis and all patients' follow-up is not complete (results for primary outcome was available for 92% of patients but the full follow-up form was only available for 79% of patients).

Study registration

All trial registration records were available. Five trials were retrospectively registered (Hermine CORIMUNO-19 2020; Lescure 2021; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021). The delay between the registration and the onset of the study was two days (Hermine CORIMUNO-19 2020; Stone 2020), three days (Lescure 2021), 15 days (Salvarani 2020), and 19 days (Veiga TOCIBRAS 2021).

Settings

All trials included were multicentre trials (6 to 65 centres); they were conducted in Brazil (Veiga TOCIBRAS 2021), China (Wang 2020), France (Hermine CORIMUNO-19 2020), Italy (Salvarani 2020), UK (Horby RECOVERY 2021), USA (Stone 2020), UK; and four were multi-country trials (Gordon REMAP-CAP 2021; Lescure 2021; Salama EMPACTA 2020; Rosas COVACTA 2021). They were performed between February 2020 and January 2021, with a mean duration of fifteen weeks (range three to 41). All participants were recruited from a hospital inpatient setting.

Characteristics of participants

We included a total of 6896 participants (10 RCTs) in the analysis of this review. Overall, 6428 participants (nine RCTs) were included in the analysis comparing tocilizumab with control; 880 participants (two RCTs) were included in the analysis comparing sarilumab with control. The mean age range varied from 56 to 65 years; 4572/6896 (66.3%) were men.

Participants had mild to critical disease in one RCT (N = 452) (Rosas COVACTA 2021), mild to severe diseases in two RCTs (N = 625) (Salama EMPACTA 2020; Stone 2020), moderate to severe disease in two RCTs (N = 196) (Hermine CORIMUNO-19 2020; Wang 2020), moderate to critical disease in three RCTs (N = 4665) (Horby RECOVERY 2021; Lescure 2021; Veiga TOCIBRAS 2021), severe disease in one RCT (N = 158) (Salvarani 2020), and severe to critical disease in one RCT (N = 826) (Gordon REMAP-CAP 2021). Inflammation makers varied but was high in most trials.

The percentage of participants on oxygen at baseline but not intubated was 56% (Rosas COVACTA 2021), 71% (Gordon REMAP-CAP 2021), 84% (Stone 2020), 84% (Veiga TOCIBRAS 2021), 86% (Horby RECOVERY 2021), 87% (Lescure 2021), 88% (Salama EMPACTA 2020), 100% (Hermine CORIMUNO-19 2020; Wang 2020). One trial did not provide this information (Salvarani 2020). Five trials reported the percentage of patients that were intubated at baseline: 12% (Lescure 2021), 14% (Horby RECOVERY 2021), 16% (Veiga TOCIBRAS 2021), 29% (Gordon REMAP-CAP 2021) ,and 37% (Rosas COVACTA 2021). In the other trials, no patient was intubated at baseline (a single patient intubated at baseline in the control group in Stone 2020).

Details of the interventions

Eight trials assessed tocilizumab compared with standard of care alone or with placebo, one study assessed tocilizumab and sarilumab compared with standard of care, and one trial compared two regimens of sarilumab versus placebo. For the analysis, the two arms were merged.

Seven trials evaluated tocilizumab 8 mg/kg by infusion for one day (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021); the dose was adapted to patients' weight

according to an algorithm in one trial (Horby RECOVERY 2021), and one evaluated a lower dose of 400 mg by infusion for one day (Wang 2020). A second infusion was allowed in six trials (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Rosas COVACTA 2021; Salvarani 2020; Wang 2020).

In Gordon REMAP-CAP 2021, participants received sarilumab at 400 mg by infusion for one day. In Lescure 2021, participants received sarilumab at 200 mg or 400 mg by infusion for one day with an option for a second dose within 24 to 48 hours.

The comparator was standard care with placebo in four trials (Lescure 2021; Rosas COVACTA 2021; Salama EMPACTA 2020; Stone 2020), and the standard of care in the other six (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Salvarani 2020; Veiga TOCIBRAS 2021; Wang 2020).

The use of steroids at baseline was reported in eight trials (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Lescure 2021; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021). Three trials reported that more participants received steroids in the control group (Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020). There was some cross-over planned in the protocol in one trial (Salvarani 2020), with 22% of participants in the control arm receiving the experimental treatment.

Funding and conflict of interest

Three trials were funded by public/non-profit sources (Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Wang 2020), four received mixed funding (Gordon REMAP-CAP 2021; Rosas COVACTA 2021; Salvarani 2020; Veiga TOCIBRAS 2021), and three were funded by the pharmaceutical industry (Lescure 2021; Salama EMPACTA 2020; Stone 2020). All authors reported their conflict of interests. The authors of seven trials declared conflicts of interest (Gordon REMAP-CAP 2021; Lescure 2021; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021), whilst in three studies (Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Wang 2020), all authors declared that they had no conflicts.

Excluded studies

We excluded a total of 269 reports; 231 were RCTs evaluating other interventions and consequently included in the COVID-NMA platform (covid-nma.com); 38 full-text reports (36 RCTs) were excluded from the COVID-NMA platform. We provided details on the reasons for exclusions in Characteristics of excluded studies.

Ongoing studies

We identified 42 trials from registries, search data: up to 11 February 2021. After contacting the investigators, we were informed that three of them were cancelled (two evaluating tocilizumab and one clazakizumab). More details are available in Appendix 4 and Appendix 5

Tocilizumab

Of the 20 unpublished trials assessing tocilizumab, five trials were completed without results available (732 participants planned); five were terminated without results available, eight were ongoing (1976 participants), two are not yet recruiting (204 participants planned).

Sarilumab

We identified two completed trials without results available (859 participants planned), three terminated without results available and six ongoing trials (857 participants planned).

Clazakizumab

Five trials are ongoing (270 participants planned) and one is not recruiting (30 participants planned).

Olokizumab

We identified one completed trial without results available (372 participants planned) and one not recruiting (376 participants planned).

Siltuximab

We identified one ongoing trial (342 participants planned).

Levilimab

We identified one completed trial without results available (206 participants planned).

Risk of bias in included studies

The‘Risk of bias' assessment summarizes the 'Risk of bias' assessment by outcome.

The‘Risk of bias' assessments for each outcome are summarised in Table 1; Table 2; Table 3; Table 4; Table 5; Table 6; Table 7; Table 8; Table 9; Table 10; Table 11; Table 12; Table 13; Table 14 and Table 15.

Risk of bias arising from the randomization process

Randomisation was described adequately and was appropriate in nine trials (Hermine CORIMUNO-19 2020; Gordon REMAP-CAP 2021; Horby RECOVERY 2021; Lescure 2021; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021). There were some concerns in one trial because the method used to conceal the allocation of treatment was unclear (Wang 2020). There was no imbalance in baseline data that indicate problem with the randomization process.

Risk of bias due to deviations from intended interventions

We judged the risk of bias due to deviation from intended interventions as low for all the outcomes reported in four blinded trials (Horby RECOVERY 2021; Lescure 2021; Rosas COVACTA 2021; Stone 2020).

However, this domain was rated as some concerns for all the outcomes reported in five unblinded trials (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Salvarani 2020; Veiga TOCIBRAS 2021; Wang 2020). In Hermine CORIMUNO-19 2020, cointerventions were reported but not balanced. Particularly steroids were more frequently provided in the standard of care group. This deviation could affect the outcome. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. In Salvarani 2020, 23% of participants allocated to standard care arm received tocilizumab mainly because of clinical worsening. This decision was planned in the protocol. Nevertheless, it could have been influenced by the trial context and this domain was consequently rated as some concerns. These deviations would be responsible for an

underestimation of the treatment effect. Other trials were rated as some concern because co-interventions were not completely reported (Gordon REMAP-CAP 2021; Veiga TOCIBRAS 2021; Wang 2020).

Finally, Salama EMPACTA 2020 was rated as some concern for important outcomes because participants who did not receive the drug (10 versus one) were excluded from the analysis post-randomisation.

Of note, in Horby RECOVERY 2021, 17% of participants allocated to tocilizumab did not receive the treatment allocated. We considered this deviation probably did not arise because of the trial context and assessed the domain as low risk.

Risk of bias due to missing outcome data

We judged the risk of bias due to incomplete outcome data as low for all trials and all outcomes since there was no or a low amount of missing data in the included trials. We rated reports of preliminary analyses with missing information, because the follow-up was not complete, as low risk of bias.

Risk of bias in the measurement of the outcome

We judged risk of bias as low for all outcomes in the four blinded trials (Lescure 2021; Rosas COVACTA 2021; Salama EMPACTA 2020; Stone 2020). In the six open trials, we considered risk of bias low for observer-reported outcomes not involving clinical judgement (i.e. mortality, WHO score 7 and above, time to death and time to WHO score 7 and above) (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Salvarani 2020; Veiga TOCIBRAS 2021; Wang 2020). In contrast, there were some concerns for the outcomes that could be potentially influenced by knowledge of the intervention assignment (i.e. clinical improvement, time to clinical improvement, adverse events and serious adverse events) (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Salvarani 2020; Veiga TOCIBRAS 2021; Wang 2020).

Risk of bias in the selection of the reported results

The protocol was available in seven trials (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021). In three trials, neither the protocol or the statistical analysis plan was available (Lescure 2021; Rosas COVACTA 2021; Wang 2020).

Overall, seven trials were judged as low risk of bias in this domain for all outcomes (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Rosas COVACTA 2021; Salama EMPACTA 2020; Stone 2020; Veiga TOCIBRAS 2021). This domain was rated as some concern for the outcome adverse event and serious adverse event in one trial (Wang 2020), clinical improvement and time to clinical improvement in one trial (Salvarani 2020), and for all-cause mortality D60 in one trial (Lescure 2021).

Bias due to missing results in the synthesis

We present a matrix indicating the availability of trial results for critical and important outcomes of the review in Appendix 7. Eight trials reported or provided results of all the review outcomes as pre-specified in the trial registry. We identified bias due to missing results in the synthesis of the tocilizumab comparison for the critical outcome all-cause mortality at D28 (Wang 2020) and in the synthesis of the sarilumab comparison for the critical outcome clinical improvement at D28 (Lescure 2021), as the outcomes were specified in the registry but not reported in the corresponding trial report.

Nine registered trials are completed but not yet published, the dates of completion range between 24 July 2020, and 10 December 2020; one of these trials is completed according to the response received from the authors but we are unaware of the completion date (NCT04479358), two other trials are reported as completed in the registry, but date of completion was not reported. The delay of publication since study completion ranged between 63 days and 202 days.

Effects of interventions

See: **Summary of findings 1** Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19; **Summary of findings 2** Sarilumab compared to standard care for severe/critical COVID-19

Comparision 1. Tocilizumab versus standard of care/placebo

We report the certainty evidence for the critical and for important outcomes in Summary of findings 1

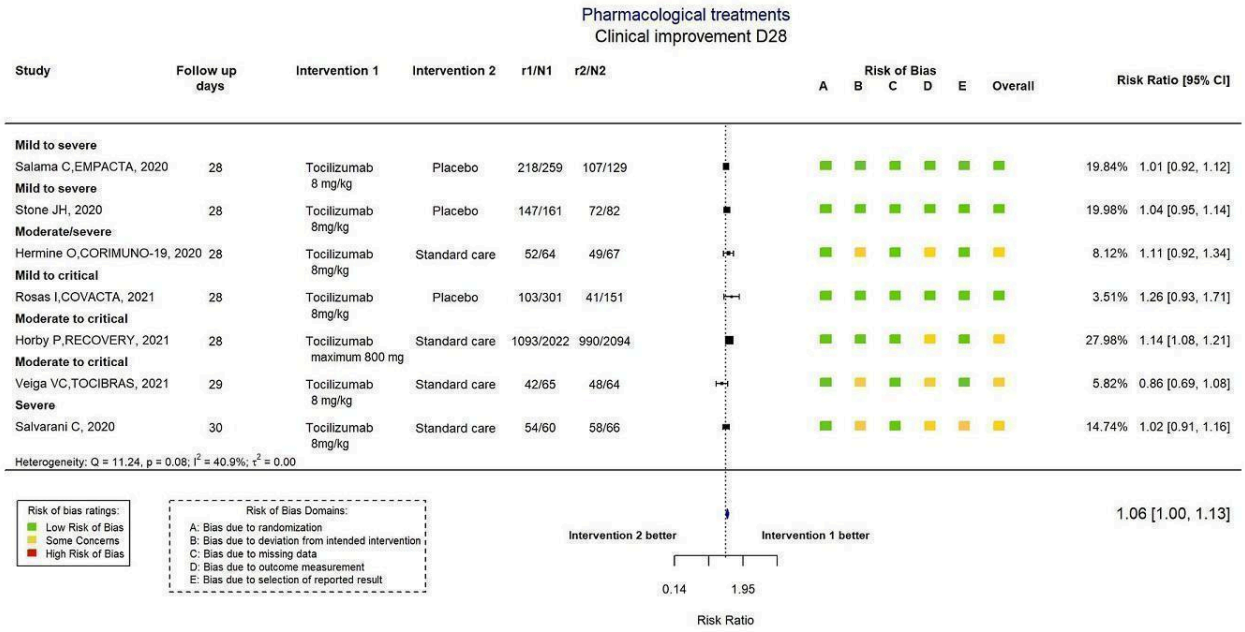
Critical outcomes

Clinical improvement

Clinical improvement was defined as hospital discharge (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Salama EMPACTA 2020; Salvarani 2020; Veiga TOCIBRAS 2021), or as an improvement from baseline by at least two categories on a 7-category ordinal scale (Rosas COVACTA 2021; Stone 2020).

The proportion of participants achieving improvement at D28 was reported in seven RCTs (5585 participants) (Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021). Tocilizumab probably results in little or no increase in clinical improvement at D28 (risk ratio (RR) 1.06, 95% confidence interval (CI) 1.00 to 1.13; I^2 = 40.9%; 7 RCTs; 5585 participants; absolute effect: 31 more per 1000 (from 0 fewer to 67 more); moderate-certainty evidence) (Figure 2). However, we cannot exclude that some subgroup of patients could benefit from the treatment. We did not obtain data for longer-term follow-up (≥ D60).

Figure 2. Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19: Clinical improvement D28

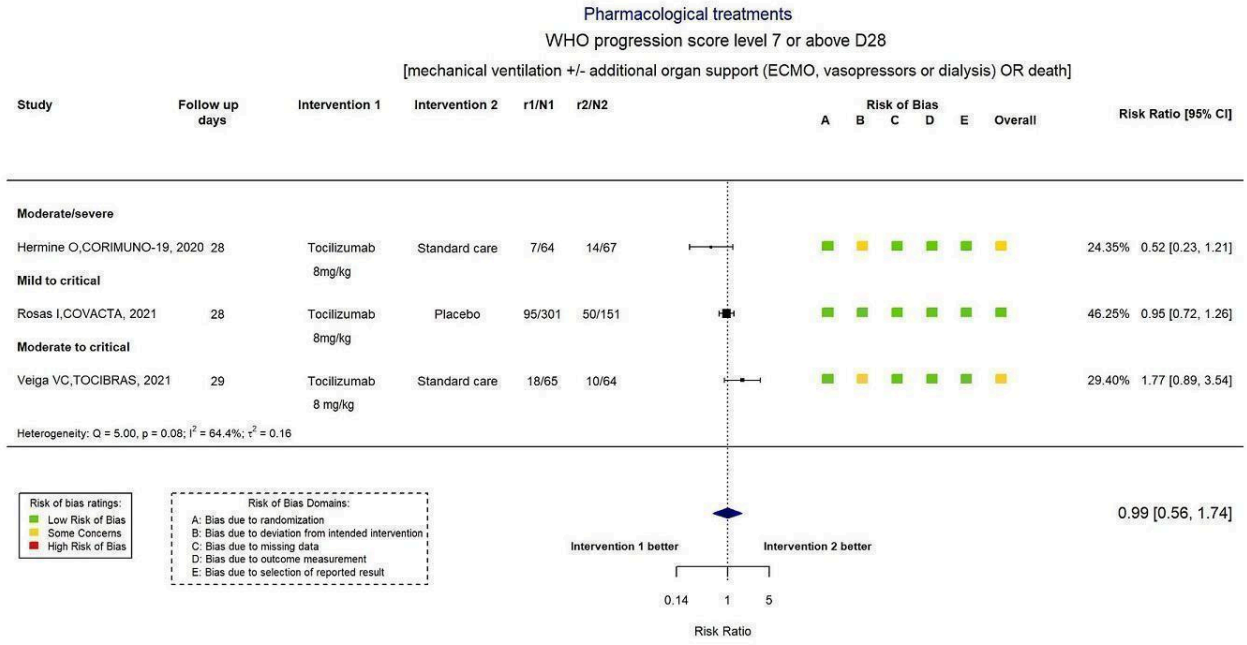


WHO Clinical Progression Score of level 7 or above (i.e. the proportion of participants with mechanical ventilation +/- additional organ support or death)

Three RCTs (712 participants) reported the proportion of participants with mechanical ventilation or death at D28 (Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Veiga TOCIBRAS 2021).

Overall, the evidence is uncertain for the effect of tocilizumab on the proportion of participants with a WHO Clinical Progression Score of level 7 or above at D28 (RR 0.99, 95% CI 0.56 to 1.74; I^2 = 64.4 %; 3 RCTs, 712 participants; low-certainty evidence) (Figure 3). We did not obtain data for longer-term follow-up (≥ D60).

Figure 3. Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19: WHO progression score (level 7 or above) D28

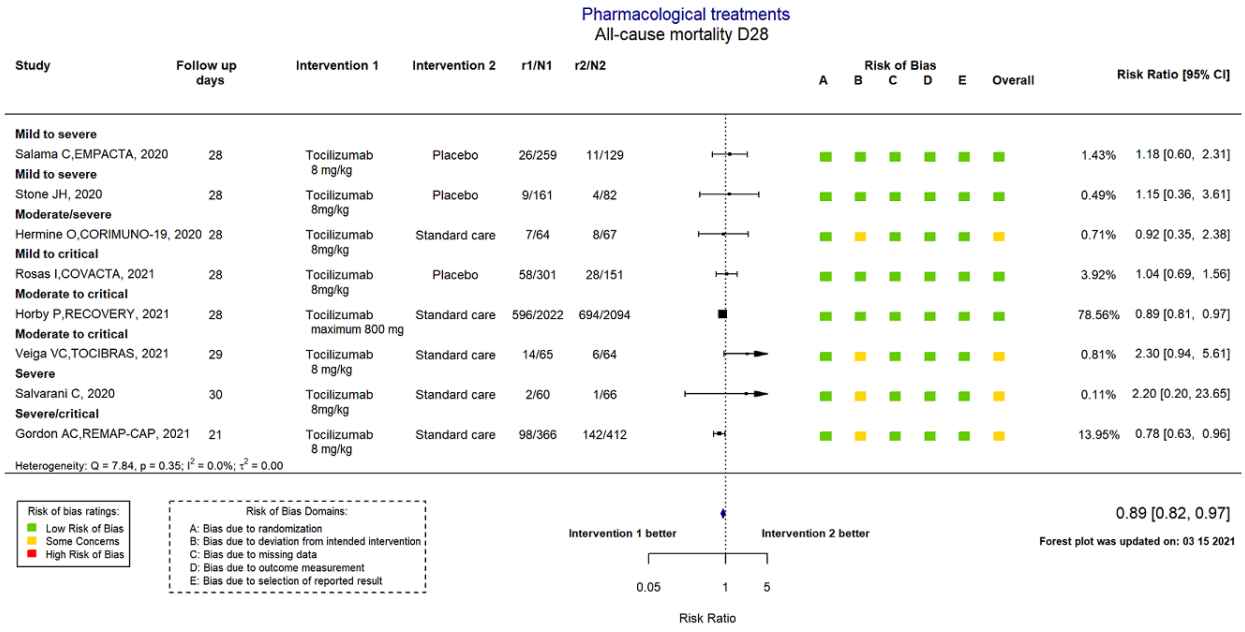


All-cause mortality

Eight RCTs (6363 participants) reported all-cause mortality at D28 (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021); two RCTs (518 participants) at ≥ D60 (Hermine CORIMUNO-19 2020; Salama EMPACTA 2020).

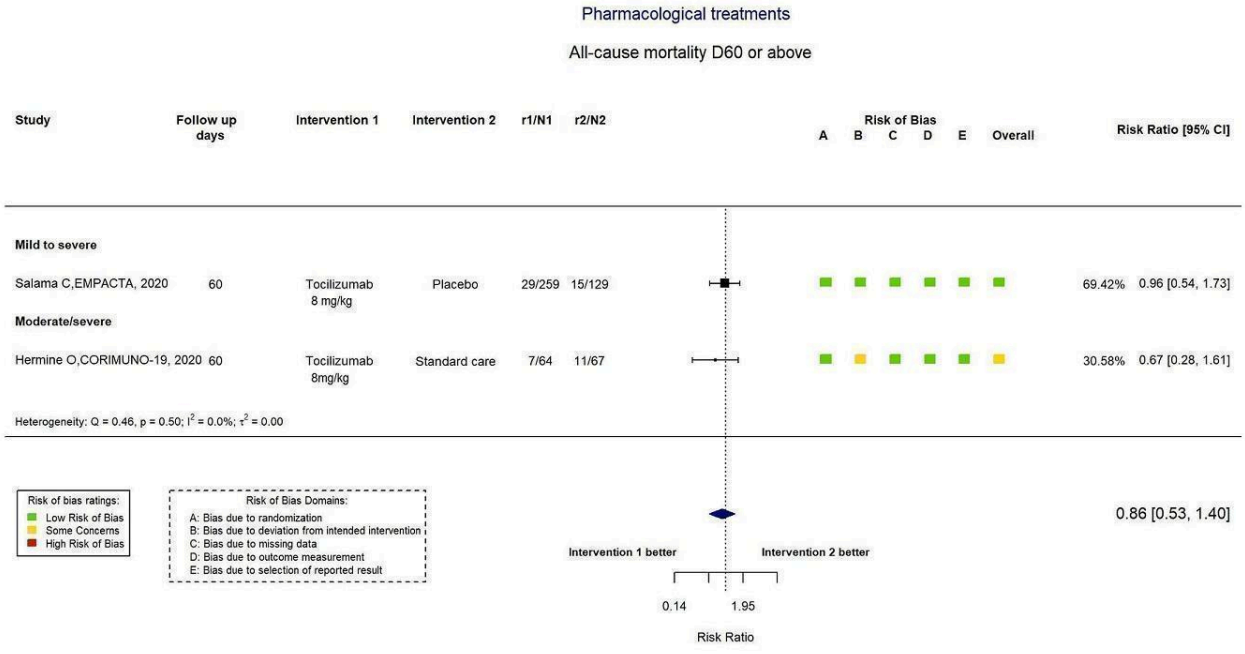
Tocilizumab reduces all-cause mortality at D28 compared with standard care alone or with placebo (RR 0.89, 95% CI 0.82 to 0.97; I^2 = 0.0%; 8 RCTs, 6363 participants; absolute effect 32 fewer per 1000 (from 52 fewer to 9 fewer); high-certainty evidence) (Figure 4).

Figure 4. Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19: All-cause mortality D28



The evidence of an effect of tocilizumab on all-cause mortality is uncertain at ≥ D60 (RR 0.86, 95% CI 0.53 to 1.40; I^2 = 0.0%; 2 RCTs; 519 participants; low-certainty evidence) (Figure 5).

Figure 5. Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19: All-cause mortality D60 or above

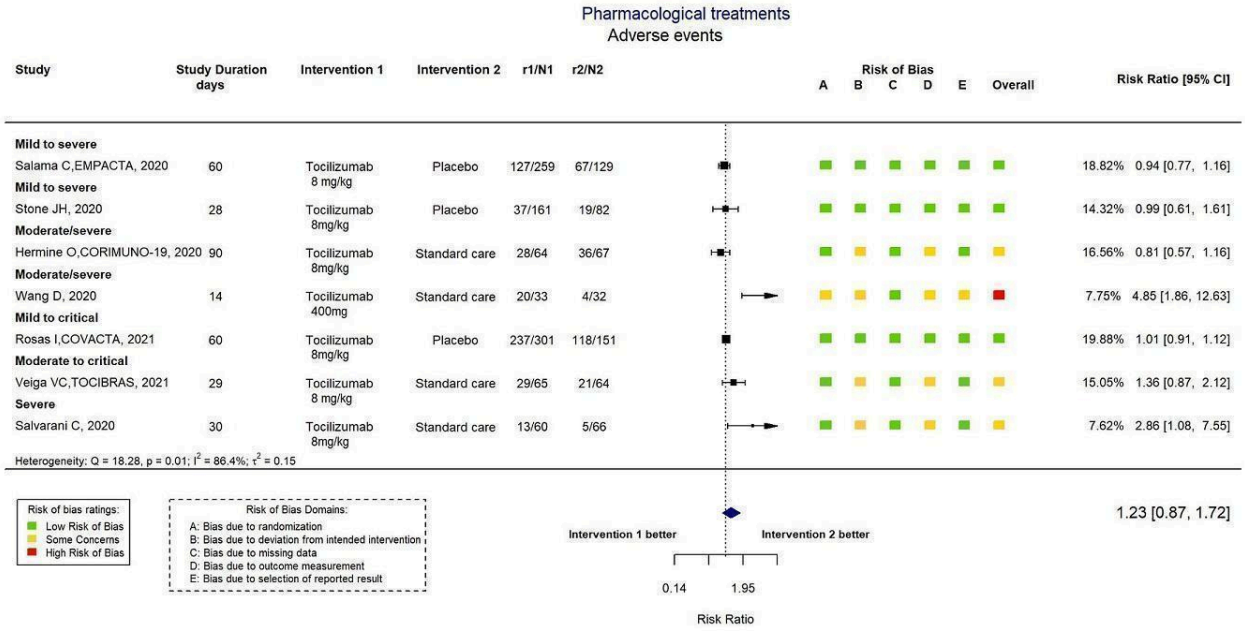


Adverse events (AEs)

AEs were assessed by spontaneous reporting (Wang 2020), active monitoring (Salvarani 2020; Stone 2020), and unknown methods in five RCTs (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020; Veiga TOCIBRAS 2021).

AEs were reported in seven RCTs (1534 participants) (Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021; Wang 2020). The evidence comparing tocilizumab with standard care alone or with placebo on adverse events is very uncertain (RR 1.23, 95% CI 0.87 to 1.72; I^2 = 86.4%; 7 RCTs, 1534 participants; very low-certainty evidence). We explored the sources of heterogeneity in the sensitivity analysis (Figure 6).

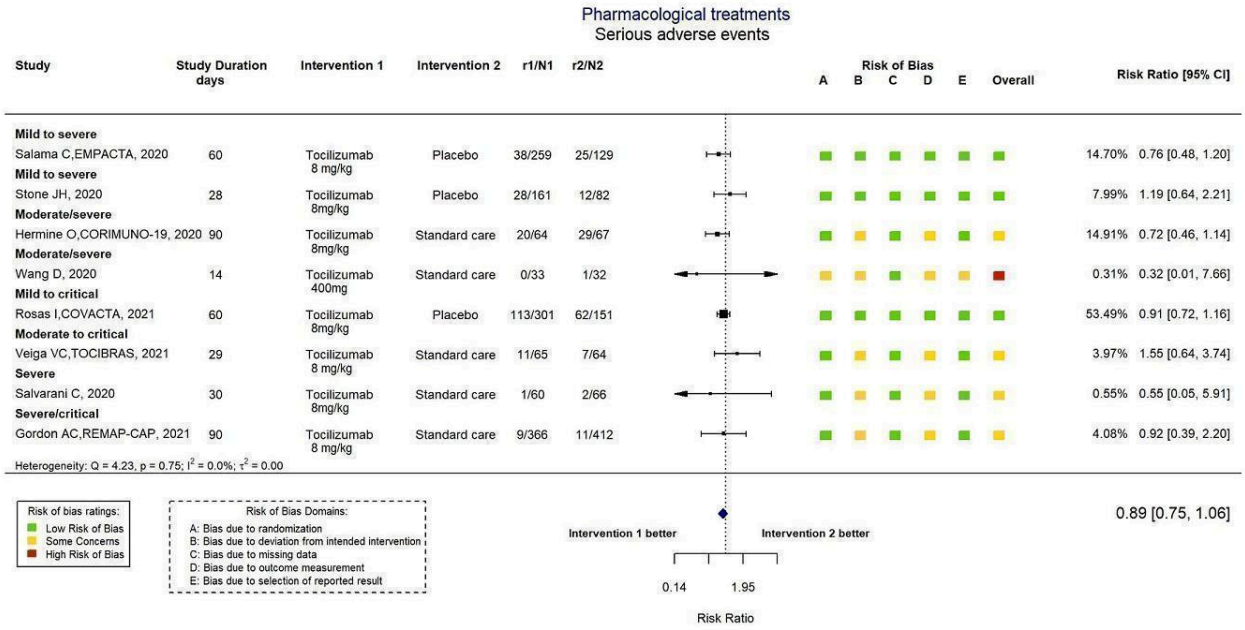
Figure 6. Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19: Adverse events



Serious adverse events (SAEs)

SAEs were reported in eight RCTs (2312 participants) (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021; Wang 2020). Tocilizumab probably results in slightly fewer SAEs than standard care alone or with placebo (RR 0.89, 95% CI 0.75 to 1.06; I^2 = 0.0%; 8 RCTs, 2312 participants; moderate-certainty evidence). However, the confidence intervals are consistent with no effect (Figure 7).

Figure 7. Tociliuzumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19: Serious adverse events



Important outcomes

(Table of results for tocilizumab versus placebo or standard care: important outcomes reported in Appendix 8.)

Time to clinical improvement

This outcome was reported in six RCTs (1992 participants) (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020). Tocilizumab probably increases the number of people who achieve clinical improvement compared with standard care alone or with placebo at a specific time point up to D28 to 90 (HR 1.23, 95% CI 1.08 to 1.39; I^2 = 28.3%; 6 RCTs, 2118 participants; moderate-certainty evidence).

Time to WHO Clinical Progression Score of level 7 or above

This outcome was reported in three RCTs (762 participants) (Hermine CORIMUNO-19 2020; Salama EMPACTA 2020; Stone 2020). Tocilizumab probably reduces the number of people who reach the WHO Clinical Progression Score of level 7 or above compared with standard care alone or with placebo at a specific time point up to D28 to 90 (HR 0.62, 95% CI 0.42 to 0.91; I^2 = 0.0%; 3 RCTs, 762 participants; moderate-certainty evidence).

Time to death

This outcome was reported in three RCTs (1152 participants) (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Stone 2020). The evidence for an effect of tocilizumab compared with standard care alone or with placebo on time to death is uncertain (HR 0.65, 95% CI 0.51 to 0.83; I^2 = 0.0%; 3 RCTs; 1152 participants; low-certainty evidence).

Comparison 2. Sarilumab versus standard of care/placebo

A three-arm trial (n = 420) (Lescure 2021), and one platform trial reported on the comparison of sarilumab (n = 48) with standard care (n = 412) (Gordon REMAP-CAP 2021). We report the certainty evidence for the critical and for important outcomes in Summary of findings 2.

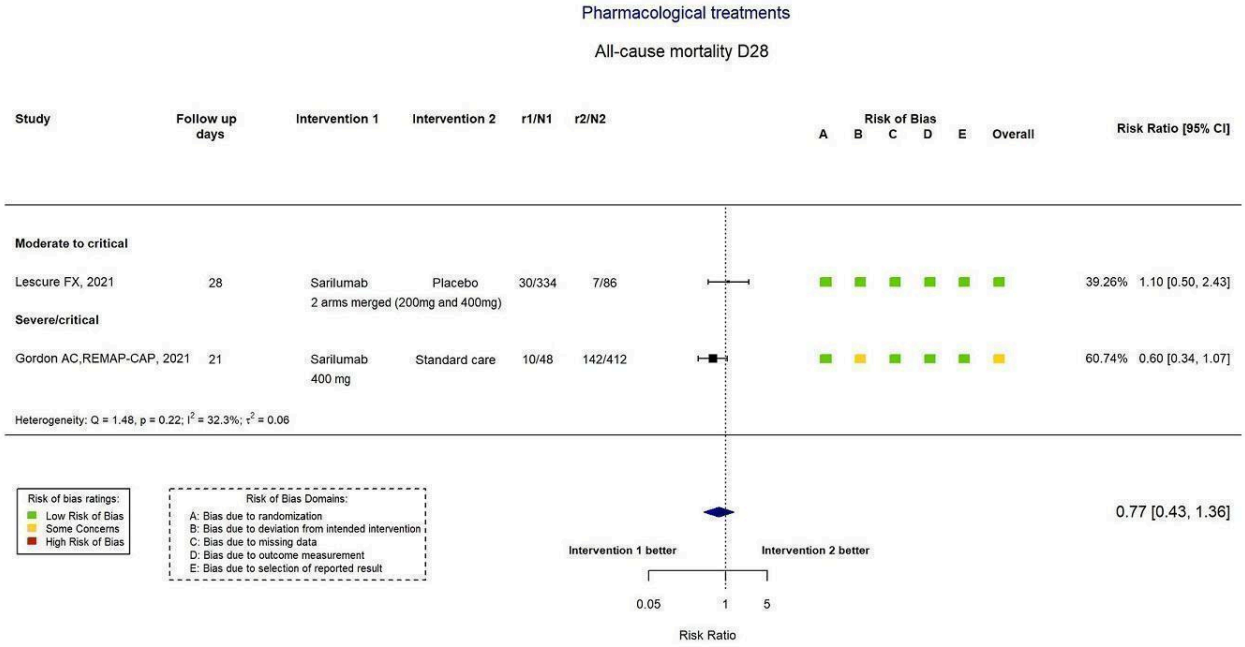
Critical outcomes

No data are available for clinical improvement (D28, ≥ D60), or WHO Clinical Progression Score of level 7 or above (D28, ≥ D60).

All-cause mortality

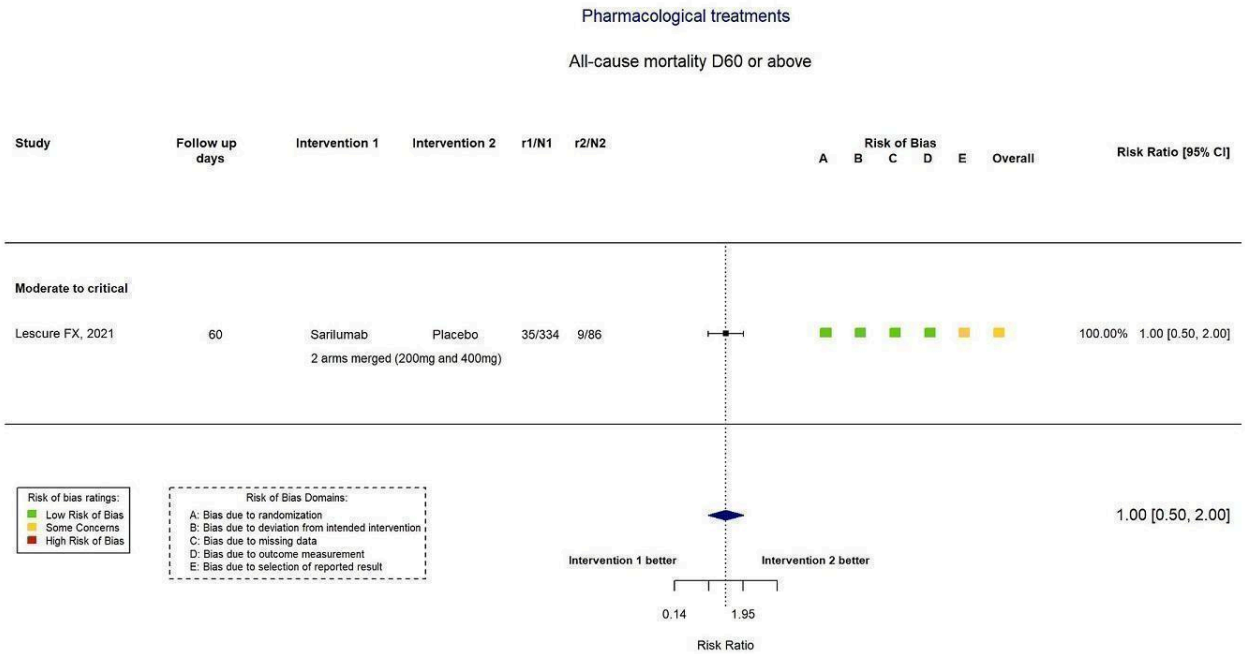
The evidence for an effect of sarilumab compared with standard care alone/with placebo on all-cause mortality at D28 is uncertain (RR 0.77, 95% CI 0.43 to 1.33; 2 RCTs, 880 participants; low-certainty evidence) (Figure 8).

Figure 8. Sarilumab compared to standard care for severe/critical COVID-19: All-cause mortality D28



The evidence for an effect of sarilumab compared with standard care alone/with placebo on all-cause mortality at ≥ D60 is uncertain (RR 1.00, 95% CI 0.50 to 2.00; 1 RCT, 420 participants; low-certainty evidence) (Figure 9).

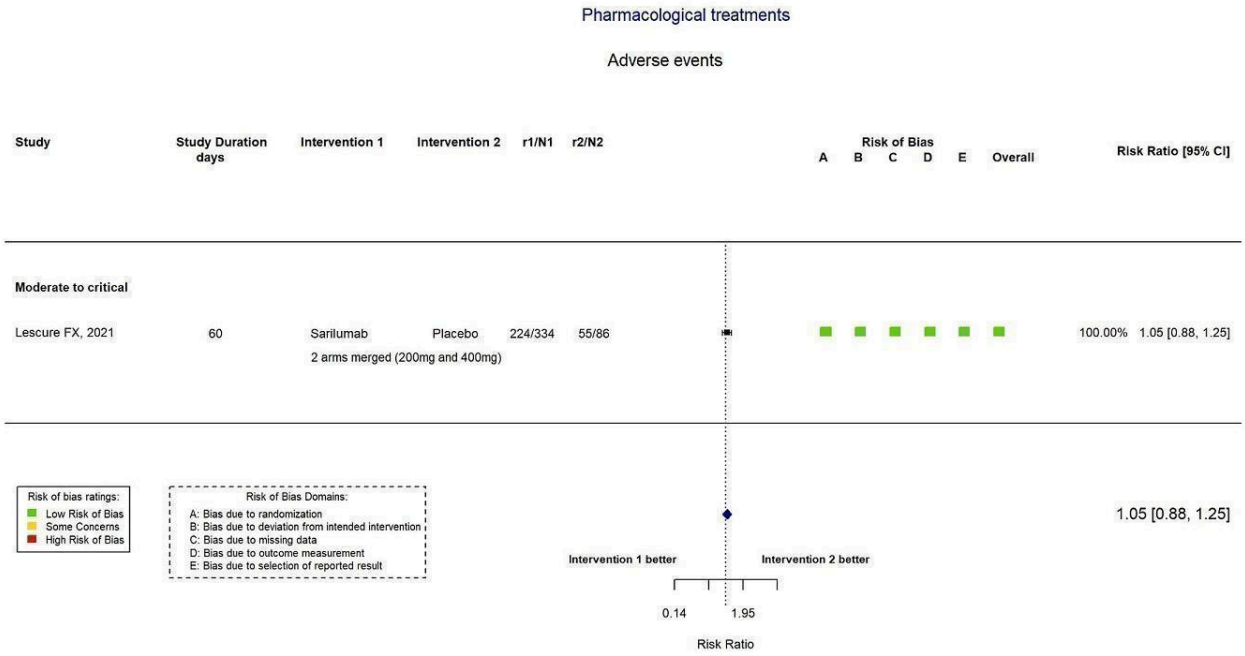
Figure 9. Sarilumab compared to standard care for severe/critical COVID-19:All-cause mortality D60 or above



Adverse events

Sarilumab is not likely to results in an increase in adverse events (RR 1.05, 95% CI 0.88 to 1.25; 1 RCT, 420 participants; absolute effect 32 more per 1000 (from 77 fewer to 160 more) ; moderate-certainty evidence). However, an important increase cannot be excluded (Figure 10).

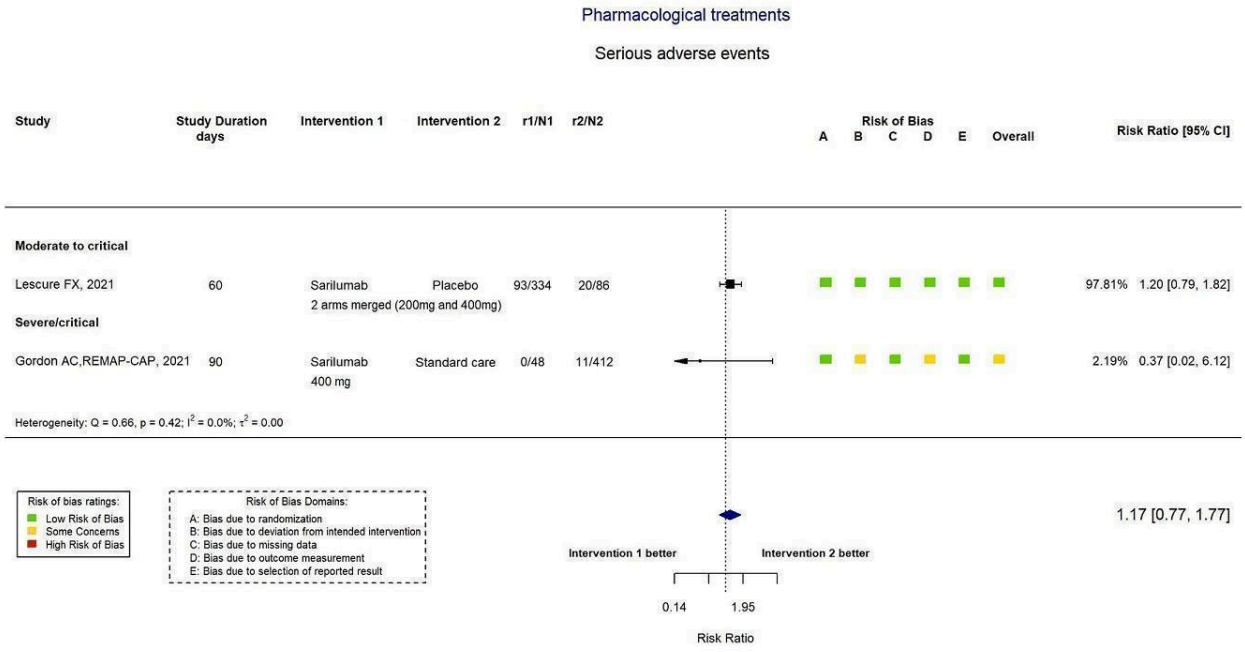
Figure 10. Sarilumab compared to standard care for severe/critical COVID-19: Adverse events



Serious adverse events

The evidence for an effect of sarilumab compared with standard care alone on serious adverse events is uncertain (RR 1.17, 95% CI 0.77 to 1.77; 2 RCTs, 880 participants; low-certainty evidence) (Figure 11).

Figure 11. Sarilumab compared to standard care for severe/critical COVID-19:Serious adverse events



Important outcomes

(Table of results for sarilumab versus placebo or standard care: important outcomes reported in Appendix 9.)

No data are available for time to WHO Clinical Progression Score of level 7 or above.

Time to clinical improvement

The evidence for an effect of sarilumab compared with standard care alone/placebo on time to clinical improvement is uncertain (hazard ratio (HR) 1.28, 95% CI 0.88 to 1.87; 2 RCTs, 880 participants; low-certainty evidence).

Time to death

The evidence for an effect of sarilumab compared with standard care alone/placebo on time to death is uncertain (HR 0.55, 95% CI 0.33 to 0.91; 1 RCT, 460 participants; low-certainty evidence).

Investigation of heterogeneity

The limited number of RCTs that provided results and the absence of variation across trials in some variables such as age and gender prevented us from performing all pre-planned subgroup analyses (see Differences between protocol and review). Some subgroup analyses were possible only for the comparisons evaluating tocilizumab. The results are available at https://zenodo.org/record/4605399#.YE9-Oi3pOfQ. We were able to explore the impact of trial location (multi-national/national) and we also considered two post-hoc subgroup analyses based on the type of funding and the presence of conflict of interest. Two of these characteristics appeared to have a substantial effect on the results based on the visual inspection of the forest plots and the test for subgroup differences: the conflict of interest of the trials and the type of funding. However, it is unclear whether the two characteristics had a real impact on the results as the summary effect in the subgroup including the Horby RECOVERY 2021 trial was mainly driven by this trial.

Sensitivity analysis

Sensitivity analyses were only possible for the comparison tocilizumab versus controls. With the exception of mortality, results were consistent when considering only trials reported as peer-reviewed article. As noted with subgroup analysis, the difference in effect estimates when restricting to peer reviewed articles likely reflects the dominance of Horby RECOVERY 2021 in the analysis. The exclusion of one trial conducted in China (Wang 2020), judged as high risk of bias did not change the results. However, it led to an important reduction of the heterogeneity for the outcome adverse events. We also decided post-hoc to check the robustness of results after excluding the trial (Rosas COVACTA 2021), that involved participants ranging from mild to critical disease. No important discrepancies in the summary results were observed when we used the number analyzed in the RCTs instead of the number randomised as denominator.

DISCUSSION

Summary of main results

This review aimed to assess the effectiveness and safety of IL-6 blocking agents for COVID-19. We identified 10 RCTs with reported results. Participants were mainly patients with moderate-severe disease. Three trials were reported as preprints (Horby RECOVERY 2021; Lescure 2021; Wang 2020). Four trials did not achieve their targeted sample size (Gordon REMAP-CAP 2021; Salvarani 2020; Veiga TOCIBRAS 2021; Wang 2020).

Our results suggest that on average tocilizumab reduces all-cause mortality at D28 compared to standard care alone or placebo. Results of important outcomes (time to clinical improvement, time to WHO progression score level 7 or above and time to death) were consistent with a beneficial effect of tocilizumab. Nevertheless, tocilizumab probably results in little or no increase in the outcome clinical improvement defined as hospital discharge or improvement on the scale used by trialists at Day D28. The discrepancy in these results could be related to the large variation in the information size across the outcomes. The beneficial effect of tocilizumab has been debated because of the important discrepancies in trial results. Several explanations for these discrepancies were discussed, particularly differences in cointerventions, particularly steroid, timing of treatment, severity of the disease, participants pattern of immune reaction (McCreary 2021). With the data available, we were not able to explore heterogeneity. Individual patient data meta-analyses are needed to be able to identify which patients are more likely to benefit from this treatment.

Regarding safety outcomes, tocilizumab probably slightly reduces serious adverse events. Evidence for its effect on all other critical outcomes was of low or very low certainty.

Evidence on the impact of sarilumab on critical outcomes was of low certainty for most outcomes.

Overall completeness and applicability of evidence

We identified 49 registered RCTs evaluating IL-6 blocking agents; only 10 had results available. All RCTs with results were multicentre and three involved several countries. We identified nine completed trials (total planned sample size 2169 participants) without results available, seven terminated trials without results available, 19 ongoing trials and four not recruiting.

The interpretation of the results of this review should be made with caution. Although participants included in these trials required oxygen or were intubated, disease severity was were heterogeneous. Four trials involved participants with critical disease (Gordon REMAP-CAP 2021; Horby RECOVERY 2021; Rosas COVACTA 2021; Veiga TOCIBRAS 2021). The severity of the disease could be an important effect modifier. Similarly, markers of inflammation (C-reactive protein (CRP)) varied between trials. However, because of the limited number of trials, heterogeneity and the impact of effect modifiers could not be explored adequately through subgroup analysis or meta-regression. There was also heterogeneity in the use of steroid that became standard care over time. In some trials the treatment effect could be underestimated because of imbalances in the use of steroids (Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020), or planned cross-over from the control group to active treatment (Salvarani 2020). Individual participant data meta-analysis would enable a more definitive investigation of heterogeneity and help to establish who would likely benefit most from interleukin 6 blocking agents.

Considering the amount of awaiting data, the conclusions of subsequently updated reviews may allow for a better judgement regarding the effectiveness and safety of IL-6 blocking agents.

Quality of the evidence

Overall, for tocilizumab, the certainty of the evidence ranged from very low for one critical outcome (adverse events), low for two critical outcomes (WHO Clinical Progression Score (level 7 or above) at D28, all-cause mortality at D60 or above) and one important outcome (time to death), moderate for two critical outcomes (clinical improvement at D28, serious adverse events) and two important outcomes time to clinical improvement and time to WHO Clinical Progression Score (level 7 or above)), and high for one critical outcome (all-cause mortality D28).

For sarilumab the certainty of the evidence was low for all outcomes except adverse events (moderate-certainty evidence).

Reasons for downgrading the certainty of evidence were risk of bias, primarily due to some concerns about deviation from intended interventions and outcome measurement; imprecision, and inconsistency (see Summary of findings 1; Summary of findings 2).

Potential biases in the review process

We followed the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). Several potential biases in the review process were minimised. First, the search strategy was peer-reviewed. We initially performed a thorough search in several electronic databases. Then, we evaluated the L-OVE platform and the Cochrane clinical trial registry and showed searches on these platforms provided 100% sensitivity on the identification of COVID-19 RCTs with considerable reduction in workload. Our search strategy was consequently modified. Second, all data were extracted in duplicate with consensus. Third, to increase our review's informative value, we are tracking all registered trials in a living mapping. This allows investigators to be contacted to obtain an update on their trial status and inform them of our outcomes of interest. Finally, the review is updated continually. We search for new trials every working day, collect data and update the syntheses once a week. All updates of this review will be available on the COVID-NMA platform (covid-nma.com).

However, important methodological issues arose. Indeed, COVID-19 is a novel disease, and new knowledge is produced daily. Consequently, the choice of critical and important outcomes and prespecified subgroup analyses can evolve over time. Due to the lack of understanding of the disease when trials were planned, we identified a lot of heterogeneity in the outcomes assessed and the definitions used. We updated the review protocol to reduce the number of outcomes considered (Boutron 2020b).

Another consideration for this rapidly evolving field is the availability of preprint articles that have not yet undergone peer review. In this review, we also included preprints. However, we are aware of these publications' potentially differing quality and that results could change once the peer-reviewed journal publications are available (Oikonomidi 2020). To overcome this issue, we developed a preprint tracker to be informed of updates and update data collection and data analysis when a preprint is modified or published.

Furthermore, patient care and consequently the standard of care evolves over time. A given trial could be stopped early if the peak of the pandemic has passed, or with recruitment over two periods (first and second wave), management has considerably evolved.

Finally, several studies were terminated and we have no data on the number of patients included in these studies.

Agreements and disagreements with other studies or reviews

We identified 23 systematic reviews focusing on IL6-blocking agents for COVID-19. Of these, 21 systematic reviews included only observational studies or preclinical studies and two included RCTs (Khan 2021; Tleyjeh 2021); the latter is a living systematic review (Tleyjeh 2021). Further, there are currently two large ongoing network meta-analyses of COVID-19 drug treatment (Juul 2020a; Juul 2020b; Siemieniuk 2020).

AUTHORS' CONCLUSIONS

Implications for practice

On average, tocilizumab reduces all-cause mortality at day 28 (D28) and probably results in slightly fewer serious adverse events compared to standard care alone or placebo. It is likely that tocilizumab increases time to clinical improvement and decreases time to intubation or death. Nevertheless, tocilizumab probably results in little or no increase in the outcome clinical improvement (defined as hospital discharge or improvement on the scale used by trialists) at D28. The impact of tocilizumab on other outcomes is uncertain.

Evidence for an effect of sarilumab is uncertain and evidence for other anti-IL6 agents are not available.

Implications for research

With the data available, we were not able to explore heterogeneity. The severity of disease varied within the trials we included, and individual patient data meta-analyses are needed to identify which patients are most likely to benefit from this treatment.

Thirty-nine RCTs of IL-6 blocking agents with no results are currently registered, of which nine are completed and seven trials were terminated with no results available. The findings of this review will be updated as soon as new data are available on the COVID-NMA platform (http://covid-nma.com).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gordon REMAP-CAP 2021

Study characteristics	
Methods	RCT- adaptive platform trial **Blinding:** unblinded **Date of study:** from 19 April 2020 to 19 November 2020 **Location:** multicentre: Australia, Ireland, the Netherlands, New Zealand, Saudi Arabia, UK **Follow-up duration (days):** 90
Participants	**Population:** patients with confirmed or suspected COVID-19 (severe-critical) **Randomised:** 826 participants (n1 tocilizumab arm = 366/ n2 sarilumab arm = n2 = 48/ n3 control arm = 412) **Characteristics of participants** • N = 826 randomised; baseline data reported for 803 participants • Mean age: 61.4 to 63.4 years

Gordon REMAP-CAP 2021 *(Continued)*

- 583 (73%) Males
- Admitted to ICU: n = 826 (100%)
- Severity: mild: n = 0 / moderate: n = 3/ severe: n = 567 / critical: n = 233
- Patients on oxygen without intubation: n = 570 (71%); Intubated: n = 233 (29%)
- C-reactive protein (median): 130 to 150 mg/L

Inclusion criteria

- Adult patient admitted to hospital with acute illness due to suspected or proven pandemic (Covid-19) infection
- Severe disease state, defined by receiving respiratory or cardiovascular organ failure support in an ICU
- Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur

Exclusion criteria

- Death is deemed to be imminent and inevitable during the next 24 hours AND 1 or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
- Patient is expected to be discharged from hospital today or tomorrow
- More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection
- Previous participation in this REMAP within the last 90 days
- More than 24 hours has elapsed since ICU admission
- Patient has already received any dose of one or more of any form of interferon, anakinra, tocilizumab, or sarilumab during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission
- Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization
- Patient has been randomised in a trial evaluating an immune modulation agent for proven or suspected Covid-19 infection, where the protocol of that trial requires ongoing administration of study drug
- The treating clinician believes that participation in the domain would not be in the best interests of the patient
- Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known or suspected pregnancy will result in exclusion from the anakinra, IFN-β1a, tocilizumab, and sarilumab interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria
- A baselineALT or an ASP that is more than five times the upper limit of normal will result in exclusion from receiving tocilizumab or sarilumab
- A baseline platelet count < 50 x 10^9 / L will result in exclusion from receiving tocilizumab or sarilumab

Dropouts and withdrawals: n = 34/826 (4%); withdrawal due to adverse events: NR

Interventions

Interventions: tocilizumab (8 mg/kg infusion, maximum 800 mg), a 2nd infusion could be administered 12 to 24 hours after the 1st at the discretion of the treating clinician. 29% received a 2nd dose. Treatment initiated within 24 hours after starting organ support in the ICU.

Sarilumab (400 mg, IV). 90% received the drug.

Control: standard care
Definition of standard care: other aspects of patient management were provided per each site's standard of care.

Overall, > 80% of participants received corticosteroids.

Remdesivir use was recorded in 33% (265/807) of patients.

Co-interventions: steroid use at baseline or any time during the study in > 80% of participants

Gordon REMAP-CAP 2021 *(Continued)*

Outcomes	**Primary outcome of the trial:** respiratory and cardiovascular organ support-free days up to day 21 Note: the definition of clinical improvement extracted is hospital discharge
Notes	**Funding:** mixed (PREPARE consortium by the EU; FP7-HEALTH-2013-INNOVATION-1; RECOVER consortium by the EU's Horizon 2020 research & innovation programme; Australian National Health & Medical Research Council; Health Research Council of New Zealand, and the Canadian Institute of Health Research, the UK National, the Health Research Board of Ireland, the UPMC Learning While Doing Program, the Breast Cancer Research Foundation, the French Ministry of Health, the Minderoo Foundation and the Wellcome Trust Innovations Project.) **Conflict of interest:** yes. (Quote:) “Dr. Gordon reports grants from NIHR, grants from NIHR Research Professorship (RP-2015-06-18), non-financial support from NIHR Clinical Research Network, non-financial support from Roche Products Ltd, non-financial support from Sanofi (Aventis Pharma)” **Protocol:** yes, available. **Statistical plan:** yes, available **Data-sharing stated: y**es, after submission of proposal to info@remapcap.org **Overall comment:** in addition to the pre-print article, the study registry and protocol were used in data extraction and 'Risk of bias' assessment. Appendices were not available. The report contains early, preliminary results of tocilizumab and sarilumab from the Immune Modulation Therapy domain of the REMAP-CAP clinical trial (an international, adaptive platform trial); further follow-up and analysis are ongoing. As a result, long-term outcomes were not reported. (Quote:) "At a scheduled interim analysis, the independent DSMB reported that tocilizumab had met the statistical trigger for efficacy (posterior probability 99.75%, odds ratio 1.87, 95%CrI 1.20, 2.76) based on an interim analysis of patients as of October 28. As per protocol, further assignment to control closed on November 19 with randomization continuing between different active immune modulation interventions (...) Following a subsequent interim analysis, the DSMB reported that sarilumab had also met the statistical trigger for efficacy and so these results are also reported" There were no important changes from the trial registration in the population, intervention, or control treatments. (Quote:) "Investigators at each site selected a priori at least two interventions, one of which had to be control, to which patients would be randomized...Randomization to the Corticosteroid domain for Covid-19 closed on June 17, 2020.12 Thereafter, corticosteroids were allowed as per recommended standard of care." This trial was updated on 1 March 2021 after publication of the study report.

Hermine CORIMUNO-19 2020

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** from 31 March 2020 to 18 April 2020 **Location:** multicentre / France **Follow-up duration (days):** 90
Participants	**Population:** patients with COVID-19 (moderate-severe) **Randomised:** 131 participants (n1 tocilizumab arm = 64 / n2 control arm = 67) **Characteristics of participants** • N = 131

Hermine CORIMUNO-19 2020 *(Continued)*

- Mean age: 64.8 years
- 88 males
- Admitted to ICU: n = 6
- Severity: mild: n = 0 / moderate: n = 55/ severe: n =75 / critical: n = 0
- Patients on oxygen without intubation: n = 130 (100%); Intubated: n = 0
- C-reactive protein (median): 119.5 to 127.0 mg/L

Inclusion criteria

- Confirmed SARS-CoV-2 infection (positive on RT-PCR and/or typical chest CT scan);
- Requiring more than 3L/minute of oxygen;
- WHO progression scale = 5
- no NIV or high flow

Exclusion criteria

- Known hypersensitivity to tocilizumab or to any of their excipients
- Pregnancy
- Current documented bacterial infection
- Patient with any of following laboratory results out of the ranges detailed below at screening should be discussed depending of the medication:
  - absolute neutrophil count (ANC) ≤ 1.0 x 10^9/L;
  - haemoglobin level: no limitation;
  - platelets (PLT) < 50 G /L;
  - SGOT or SGPT > 5N.

Dropouts and withdrawals: 1/131(1%); 0 withdrawal due to AEs

Interventions	**Intervention:** tocilizumab (8 mg/kg infusion) on day 1, an additional fixed dose of 400 mg IV on day 3 at physician discretion. The number of patients who received 2nd dose is not reported. **Control:** standard care **Definition of standard care:** usual care (antibiotic agents, antiviral agents, corticosteroids, vasopressor support, anticoagulants) was provided at the discretion of the clinicians. **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: 21 (33%) Standard care: 41 (61%)

Outcomes	**Primary outcome of the trial:**
	
	• The 2 primary outcomes were:
	  • the proportion of patients dead or needing noninvasive or mechanical ventilation on day 4 (> 5 on the WHO-CPS); and
	  • survival with no need for noninvasive or mechanical ventilation at day 14
	
	Note: the definition of clinical improvement extracted is hospital discharge

Notes	**Funding:** public/nonprofit. (This trial was publicly funded (Ministry of Health, Programme Hospitalier de Recherche Clinique, Foundation for Medical Research (FRM), AP-HP Foundation and the Reacting program).) **Conflict of interest:** declared. No conflict of interest. Quote: “Dr Tharaux has received honorarium fees for participation on advisory boards for Retrophin Inc not related to this work. No other disclosures are reported.” **Protocol:** yes, available. **Statistical plan:** yes, available. **Data-sharing stated:** yes, with publication. philipperavaud@gmail.com

Hermine CORIMUNO-19 2020 *(Continued)*

Overall comment: in addition to the published article, the trial registry, protocol and supplemental materials and the reply provided by authors were used in data extraction and assessment of risk of bias. There were no major differences between trial registry, protocol and published article in procedures and outcomes, and no changes in treatments.

Immunotherapy co-interventions consisted of anakinra (1 participant in intervention group, 3 in control) and eculizumab (1 participant in control). Remdesivir was given to 1 participant in control group.

On 23 October 2020, we received additional information from authors on this study. This study was updated with data from contact with authors.

Horby RECOVERY 2021

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** from 14 April 2020-to 24 January 2021 **Location:** multicentre (131 centres) / UK **Follow-up duration (days):** 28
Participants	**Population:** patients with suspected or confirmed COVID-19 (moderate-critical) admitted to 131 centres in the UK **Randomised:** 4116 participants (n_1= 2022 / n_2 = 2094) **Characteristics of participants** • Mean age: 63.6 years • 2772 males • Admitted to ICU: n = NR • Severity: mild: n = 9 / moderate: n = 1868 / severe: n = 1686 / critical = 562 • Patients on oxygen without intubation: n = 3554 (86%); intubated: n = 562 (14%) • C-reactive protein (median): 143 to 144 mg/L **Inclusion criteria** • Hospitalised adults patients (including pregnant women) with clinically suspected or laboratory-confirmed SARS-CoV-2 infection • Hypoxia (oxygen saturation < 92% on air or requiring oxygen therapy); evidence of systemic inflammation (C reactive protein (CRP) ≥ 75 mg/L) • No medical history that might, in the opinion of the attending clinician, put patients at substantial risk if they were to participate in the trial **Exclusion criteria** • A specific contra-indication to 1 of the active drug treatment arms or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomization for that patient • 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 randomization to tocilizumab **Dropouts and withdrawals :** 0% dropout, withdrawal due to AEs: NR
Interventions	**Intervention:** tocilizumab (800 mg if weight > 90 kg; 600 mg if weight > 65 and ≤ 90 kg; 400 mg if weight > 40 and ≤ 65 kg; 8 mg/kg if weight ≤ 40 kg); a 2nd infusion could be administered 12 to 24 hours after the 1st)

Horby RECOVERY 2021 *(Continued)*

	Control: standard care **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: 1664 (82%) Standard care: 1721 (82%)
Outcomes	**Primary outcome of the trial** 28-day mortality Note: the definition of clinical improvement extracted is discharged alive from hospital within 28 days.
Notes	**Funding:** public/non profit (UK research and Innovation/National Institute for Health Research (NIHR); NIHR Oxford Biomedical Research Centre, Wellcome; Bill and Melinda Gates Foundation; Department for International Development; Health Data Research UK; Medical Research Council Population Health Research Unit; NIHR Clinical Trials Unit Support Funding; Abbvie (lopinavir-ritonavir); Roche Products Ltd (tocilizumab); Regeneron (REGEN-480 COV2)) **Conflict of interest:** yes, declared. The authors have no conflict of interest or financial relationships relevant to the submitted work to disclose **Protocol:** yes. In English **Statistical plan:** yes **Data-sharing stated:** yes, within 3 months of publication **Data accessibility**: ndph.ox.ac.uk/data-access **Overall comment:** in addition to the pre-print article, the study registry and protocol were used in data extraction and 'Rrisk of bias' assessment. This article is a preliminary report on the tocilizumab arm of the ongoing RECOVERY platform study after 28 days with the main analysis planned at 6 months post-randomisation. As a result, the target sample size specified in the registry was not achieved. There is no change from the trial registration in the intervention and control treatments.

Lescure 2021

Study characteristics	
Methods	RCT **Blinding:** quadruple blinding **Date of study:** from 28 March 2020 to 3 July 2020 **Location:** multicentre (45 centres) / Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain **Follow-up duration (days):** 60
Participants	**Population:** patients with confirmed (any specimen) COVID-19 (moderate-critical) admitted to 45 centres in Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain. **Randomised:** 420 participants (n_1 sarilumab 400 mg = 173/ n_2 sarilumab 200 mg = 161/ n_3 control = 86) **Characteristics of participants** • Mean age: 58 to 60 years • 261 males • Admitted to ICU: n = 148 • Severity: mild: n = 2 / moderate: n = 304/ severe: n = 60 / critical = 50 • Patients on oxygen without intubation: n = 364 (87%); Intubated: n = 50 (12%) • C-reactive protein (median): 94.6 (48.1 to 167.9) mg/L **Inclusion criteria**

Lescure 2021 *(Continued)*

- Patients aged 18 years or older at the time of signing informed consent
- Hospitalised for laboratory-confirmed SARS-CoV-2 infection in any specimen within 2 weeks prior to randomization
- Evidence of pneumonia by chest imaging or chest auscultation and no alternative explanation for current clinical presentation
- Meet criteria for severe disease (defined as administration of supplemental oxygen by nasal cannula, simple face mask, or another similar device) or critical disease (defined as need for supplemental oxygen delivered by nonrebreather mask or high-flow nasal cannula, use of invasive or noninvasive ventilation, or treatment in an ICU)

Exclusion criteria

- Patients with at least 1 of the following: in the investigator's opinion, a low probability of surviving 48 hours or remaining at the investigational site beyond 48 hours
  - Dysfunction of ≥ 2 organ systems or need for extracorporeal life support or renal replacement therapy at screening
  - Absolute neutrophil count < 2000/mm3;AST or ALT exceeding 5-fold upper limit of normal (ULN) at screening
  - Platelets < 50,000/mm3 at screening
  - Known active, incompletely treated, suspected or known extrapulmonary tuberculosis
  - Prior or concurrent use of immunosuppressants at screening, including, but not limited to, IL-6 inhibitors or Janus kinase inhibitors within 30 days of baseline; Anti-CD20 agents without evidence of B-cell recovery to baseline levels or IL-1 receptor antagonist (anakinra) within 1 week of baseline
  - Abatacept within 8 weeks of baseline; tumour necrosis factor a inhibitors within 2 to 8 weeks of baseline
  - Alkylating agents, including cyclophosphamide, within 6 months of baseline
  - Cyclosporine, azathioprine, mycophenolate mofetil, leflunomide, or methotrexate within 4 weeks of baseline
  - Intravenous (IV) immunoglobulin within 5 months of baseline
  - Use of systemic chronic (e.g. oral) corticosteroids for a condition not related to COVID-19 at doses higher than prednisone 10 mg/day or equivalent at screening
  - Suspected or known active systemic bacterial or fungal infections within 4 weeks of screening

Dropouts and withdrawals: 0% dropout, withdrawal due to AEs: NR

Interventions	**Intervention** • Sarilumab 400 mg (400 mg IV infusion, a 2nd dose could be administered 24 to 48 hours after the 1st) • Sarilumab 200 mg (200 mg IV infusion, a 2nd dose could be administered 24 to 48 hours after the 1st) **Control:** placebo **Definition of standard care:** local standard of care **Co-interventions** **Steroid use at baseline or any time during the study** Sarilumab 400 mg: 78 (45%) Sarilumab 200 mg: 58 (36%) Placebo: 39 (45%)
Outcomes	**Primary outcome of the trial** Time from baseline to clinical improvement of ≥ 2 points on a 7-point ordinal scale. Discharge prior to day 29 was considered as a 2-point improvement. Note: the definition of clinical improvement extracted is improvement from baseline by at least 2 categories on a 7-point ordinal scale
Notes	**Funding:** private (Sanofi and Regeneron Pharmaceuticals, Inc)

Lescure 2021 *(Continued)*

Conflict of interest: yes, declared. F-XL has received lecture fees from Merck Sharp & Dohme and Gilead Science. HH has nothing to disclose of relevance to this study. RF has no financial conflicts to disclose. JSL, GS, PW, NP, and OH are employees of Sanofi and may hold stock and/or stock options in the company.
Protocol: NR
Statistical plan: NR
Data-sharing stated: yes, currently available
Data accessibility: clinicalstudydatarequest.com/

Overall comment: in addition to the pre-print article, the supplementary materials, and the study registry were used in data extraction and r'Rsk of bias' assessment. Neither study protocol nor statistical analysis plan were available. There were no substantive differences between the prospective registry and the pre-print article. The study was an adaptive design and any changes in protocol versions are reported with rationales in the article. The study achieved its pre-stated sample size. As this study was conducted in 11 countries across 45 sites, standard of care may have differed (supported by concomitant medication use presented in Table S2).

Rosas COVACTA 2021

Study characteristics

Methods	RCT **Blinding:** double-blinding **Date of study:** from 3 April 2020 to 28 July 2020 **Location:** multicentre: Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, UK, USA **Follow-up duration (days):** 60
Participants	**Population:** patients with confirmed COVID-19 (mild to critical) **Randomised:** 452 participants (n1 tocilizumab arm = 301 / n2 control arm = 151) **Characteristics of participants** • N = 452 • Mean age: 60.8 years • 306 Males • Admitted to ICU: n = 247 (56%) • Severity: mild: n = 15 / moderate: n = 122/ severe: n = 133/ critical: n = 168 • Patients on oxygen without intubation n = 255 (56%); Intubated n = 168 (37%) • C-reactive protein (median): 150.3 to 157.2 mg/L **Inclusion criteria** Patients 18 years or older with severe COVID-19 pneumonia confirmed by positive polymerase chain reaction test in any body fluid and evidenced by bilateral chest infiltrates on chest x-ray or CT were enrolled. Eligible patients had blood oxygen saturation ≤ 93% or partial pressure of oxygen/fraction of inspired oxygen < 300 mm/Hg. Informed consent was obtained for all enrolled patients. **Exclusion criteria** Patients were excluded if the treating physician determined that death was imminent and inevitable within 24 hours or if they had active tuberculosis or bacterial, fungal, or viral infection other than SARS-CoV-2. **Dropouts and withdrawals** :14/452 (3%); 0 withdrawal due to AEs
Interventions	**Intervention:** tocilizumab (8 mg/kg infusion, maximum 800 mg), a second infusion could be administered 8 to 24 hours after the first) **Control:** placebo

Rosas COVACTA 2021 *(Continued)*

	Co-interventions **Steroid use at baseline or any time during the study** Tocilizumab: 57 (19%) Placebo: 41 (28%)
Outcomes	**Primary outcome of the trial** Clinical status assessed on a 7-category ordinal scale at day 28 Note: the definition of clinical improvement extracted is improvement from baseline by at least 2 categories on the ordinal scale
Notes	**Funding:** mixed (F. Hoffmann-La Roche Ltd; Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority) **Conflict of interest:** yes. (Quote:) "I.O.R. received a grant from Roche/Genentech during the conduct of the study; a grant and personal fees from Genentech outside the submitted work; and personal fees from Boehringer and Bristol-Myers Squibb outside the submitted work. A.M.'s institution received grant support from Roche/Genentech during the conduct of the study; he has received funding from the National Institutes of Health outside the submitted work and medical education from Merck and Livanova outside the submitted work." **Protocol:** yes, available **Statistical plan:** yes, available **Data-sharing stated:** yes, through vivli.org **Overall comment:** in addition to all available versions of the pre-print article, the study registry and supplementary appendix, as well as responses from contact with authors were used in data extraction and 'Risk of bias' assessment. The protocol and statistical analysis plan were not available although it was sent by authors after requested. The full data could not be accessed. Patients in the tocilizumab group received a 2nd dose only if their condition did not improve or worsened. The study achieved the target sample size prespecified in the registry. There is no change from the trial registration in the intervention and control treatments as well as primary outcome. Some secondary outcomes in the registry were not reported in the pre-print article, particularly regarding the 60-day time point as well. The sponsor (Hoffman-La Roche Ltd.) played a prominent role, with writing support for the authors provided by Sara Duggan, Ph.D., of ApotheCom, funded by F. Hoffmann-La Roche Ltd. 3 authors were employees of Roche Products Ltd. On 7 December 2020, we received additional information from authors on this study. This study was updated with data from contact with authors on 13 January 2021. This trial was updated on 1 March 2021 after publication of the study report.

Salama EMPACTA 2020

Study characteristics	
Methods	RCT **Blinding:** double-blinding **Date of study:** from 14 May 2020 to 18 August 2020 **Location:** multicentre / Brazil, Kenya, Mexico, Peru, South Africa, USA

Salama EMPACTA 2020 *(Continued)*

	Follow-up duration (days): 60
Participants	**Population:** patients with confirmed COVID-19 (mild to severe) **Randomised:** 388 participants (n1 tocilizumab arm = 259 / n2 control arm = 129) **Characteristics of participants** • N = 388 • Mean age: 55.9 years • 223 males • Admitted to ICU: n = 58 • Severity: mild: n = 35 / moderate: n = 242/ severe: n = 100/ critical: n = 0 • Patients on oxygen without intubation: n = 342 (88%); Intubated: n = 0 • C-reactive protein (median) : 124.5 to 143.4 mg/L **Inclusion criteria** • Patients ≥18 years of age (with no upper age limit) • Hospitalized with Covid-19 pneumonia confirmed by a positive polymerase chain reaction test and radiographic imaging • Blood oxygen saturation < 94% on ambient air **Exclusion criteria** • If they required continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation • If progression to death was imminent and inevitable within 24 hours as determined by the treating physician • Active tuberculosis or suspected active bacterial, fungal, or viral infection (other than SARS-CoV-2 or well-controlled HIV) • Patients with comorbidities were not excluded unless the investigator determined it would preclude safe patient participation **Dropouts and withdrawals:** 11/388 (3%); 0 withdrawal due to AEs
Interventions	**Intervention:** tocilizumab (8 mg/kg up to 800 mg max infusion) **Control:** placebo **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: 200 (77%) Placebo: 112 (87%)
Outcomes	**Primary outcome of the trial:** Mechanical ventilation (invasive mechanical ventilation or extracorporeal membrane oxygenation) or death by day 28 Note: the definition of clinical improvement extracted is improvement from baseline by at least 2 categories on the ordinal scale
Notes	**Funding:** private (Genentech, Inc.) **Conflict of interest:** yes, declared. Quote “C.S. reports personal fees from Genentech, Inc. J.H., L.Y., W.G.R., B.K., and S.V.M are employees and shareholders of Genentech, Inc. and have filed a patent for a method of treating pneumonia, including COVID-19 pneumonia, with an IL-6 antagonist.” **Protocol:** yes, available. **Statistical plan:** yes, available. **Data-sharing stated:** yes, through vivli.org/

Salama EMPACTA 2020 *(Continued)*

Overall comment: in addition to the published article, the pre-print article, study registry, protocol, statistical analysis plan and supplementary appendix were used in data extraction and 'Risk of bias' assessment. The study achieved the target sample size specified in the trial registry. There is no change from the trial registration in the intervention and control treatments. The registry and protocol version 1 primary outcome (cumulative proportion of mechanical ventilation) does not reflect the primary outcome reported in the paper and protocol version 2 (cumulative proportion of mechanical ventilation or death). Some secondary outcomes reported in the registry were not reported in the manuscript.

On 21 December 2020, we received additional information from authors on this study, we updated the study results based on authors reply. The study was also updated on 13 January 2021 with data from the New England Journal of Medicine publication.

Salvarani 2020

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** from 31 March 2020 to 11 June 2020 **Location:** multicentre / Italy **Follow-up duration (days):** 30
Participants	**Population:** patients with confirmed COVID-19 (severe) **Randomised:** 126 participants (n1 tocilizumab arm = 60 / n2 control arm = 66) **Characteristics of participants** • N = 126 • Mean/median age: 60 years • 77 males • Admitted to ICU: n = 0 • Severity: mild: n = 0 / moderate: n = 0/ severe: n = 126 / critical: n = 0 • Patients on oxygen without intubation: n = NR; Intubated: n = 0 • C-reactive protein (median): 6.5 to 10.5 mg/L **Inclusion criteria** Patients 18 years and older, with an instrumental diagnosis of COVID-19 pneumonia confirmed by a positive reverse-transcriptase polymerase chain reaction assay for SARS-CoV-2 in a respiratory tract specimen. Other inclusion criteria were the presence of acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FIO_2) ratio between 200 mm Hg and 300 mm/Hg, an inflammatory phenotype defined by a temperature greater than 38 ‘C during the last 2 days, and/or serum C-reactive protein (CRP) levels of 10mg/dL or greater and/or CRP level increased to at least 2 times the admission measurement. **Exclusion criteria included** • ICU admission • Known hypersensitivity to tocilizumab • Any condition preventing future admission to ICU, such as advanced age with multiple comorbidities, as well as the patient’s expressed will to avoid future intubation. **Dropouts and withdrawals:** 3/126 (2%); 0 withdrawals due to AEs
Interventions	**Intervention:** tocilizumab (8 mg/kg) on day 1 up to a maximum of 800 mg, followed by a 2nd dose after 12 hours **Control:** standard care

Salvarani 2020 *(Continued)*

	Definition of standard care: supportive care following the treatment protocols of each centre. All drugs were allowed but IL-1 blockers, Jak inhibitors, and tumour necrosis factor inhibitors. Steroids were allowed if already taken before hospitalization. In case of occurrence of documented clinical worsening, patients randomised in both arms could receive any therapy, including steroids, and, for patients randomised in the control arm, tocilizumab. **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: 6 (10%) Standard care: 7 (11%)

Outcomes	**Primary outcome of the trial**
	
	• Clinical worsening within 14 days since randomization, defined by occurrence of 1 of the following events:
	  ○ admission to ICU with mechanical ventilation;
	  ○ death;
	  ○ PaO_2/FIO_2 ratio > 150 mm Hg
	
	Note: the definition of clinical improvement extracted is discharge.

Notes	**Funding:** mixed (local resources, the Italian Ministry of Health and Roche) **Conflict of interest:** yes, declared. Quote "Dr Costantini reported receiving nonfinancial support (provision of experimental drug and distribution to clinical sites) from Roche during the conduct of the study. Dr Angheben reported receiving grants from Italian Ministry of Health" **Protocol: y**es, available **Statistical plan:** yes, available **Data-sharing stated:** yes, after approval of a proposal **Overall comments**: in addition to the published article, the trial registries, protocol and supplemental material were used in data extraction and assessment of risk of bias. The trial was terminated on the decision of the Scientific Committee due to lack of effect and poor enrolment because of the dramatic decrease in the incidence of the disease in Italy at the time. There were some differences between trial registration and published article in inclusion and exclusion criteria. There was no difference in study treatments between trial registration and published article.14 participants in the standard care group crossed over and received tocilizumab after clinical worsening

Stone 2020

Study characteristics	
Methods	RCT **Blinding:** double-blinding **Date of study:** from 20 April 2020 to 15 June 2020 **Location:** multicentre / USA **Follow-up duration (days):** 28
Participants	**Population:** patients with COVID-19 (mild to severe) **Randomised** 243 participants (n1 tocilizumab arm = 161 / n2 control arm = 82) **Characteristics of participants** • Mean / median age: 60 years

Stone 2020 *(Continued)*

- 141 males
- Admitted to ICU: n = 11 (4%)
- Severity: mild: n = 38 / moderate: n = 194/ severe: n = 10 / critical: n = 1
- Patients on oxygen without intubation: n = 204 (84%)
- Intubated: n = 1
- C-reactive protein (median) : 94.3 to 116 mg/L

Inclusion criteria

- Patients were eligible for enrolment if they were 19 to 85 years of age and had SARS-CoV-2 infection confirmed by either nasopharyngeal swab polymerase chain reaction or serum IgM antibody assay
- Patients had to have at least 2 of the following signs:
  - fever (body temperature > 38°C) within 72 hours before enrolment;
  - pulmonary infiltrates; or
  - a need for supplemental oxygen in order to maintain an oxygen saturation higher than 92%.
- At least one of the following laboratory criteria also had to be fulfilled:
  - C-reactive protein level higher than 50 mg per litre;
  - ferritin level higher than 500 ng per millilitre;
  - D-dimer level higher than 1000 ng per millilitre; or
  - lactate dehydrogenase level higher than 250 U per litre.

Exclusion criteria

Unable to provide verbal informed consent or have verbal agreement to participate through attestation and signature of a witness required, as outlined in the Partners IRB's Table for Consenting in COVID Research that is More than Minimal Risk. Patients between the ages of 79 and 86 will be excluded if they have:

- NYHA Class III/IV heart 32 of 92;
- pulmonary infiltrate on chest X ray;
- need for supplemental O_2 to maintain saturation > 92% AND at least 1 of the following:
  - ferritin > 500 ng/mL;
  - CRP > 50 mg/L;
  - LDH > 250 U/L.
- D-dimer > 1000 ng/mL failure, insulin-dependent diabetes mellitus, angina, or treatment of a malignancy (excluding nonmelanoma skin cancer) within 6 months
- uncontrolled bacterial, fungal, or non-COVID viral infection
- active tuberculosis (see appendix B)
- any prior investigational immunosuppressive therapy within 28-days or 3 half-lives of the agent (for instance with biologic or JAK inhibitor)
- any concurrent immunosuppressive medication that the PI believes would put the patient at higher risk
- receipt of intravenous tocilizumab for the treatment of a non-COVID condition within 3 weeks of the first COVID symptom
- history of hypersensitivity to tocilizumab
- any concurrent immunosuppressive medication that the PI believes would put the patient at higher risk
- treatment with other biologic or small-molecule immunosuppressive therapy such as IL1R-antagonism, JAK inhibition, or other agents.
- treatment with convalescent plasma
- history of diverticulitis or bowel perforation
- ANC < 500, platelets < 50,000
- AST/ALT > 5X ULN

Dropouts and withdrawals: 1/243 (1%); 0 withdrawal due to AEs

Stone 2020 *(Continued)*

Interventions	**Intervention:** tocilizumab (8 mg/kg infusion up to 800 mg max) single dose **Control:** placebo
Outcomes	**Primary outcome of the trial:** the primary outcome was intubation (or death, for patients who died before intubation) after administration of tocilizumab or placebo, assessed in a time-to-event analysis. Note: improvement was defined as an decrease in score by at least 2 points on the ordinal clinical improvement scale.
Notes	**Funding:** private (supported by Genentech) **Conflict of interest:** yes, declared. Quote: "Dr. Stone reports grants from Genentech, during the conduct of the study; grants and personal fees from Principia Biopharma and Roche, grants from Viela, personal fees from Sanofi, Chemocentryx, Celgene, Abbvie, Chugai, Grunenthal, Glaxo Smith Kline, InflaRx, INSmed, Regeneron, Roivant, outside of submitted work." **Protocol:** yes, available. **Statistical plan:** yes, available. **Data-sharing stated:** yes, following approval of proposal. **Overall comment**: in addition to the published article, the trial registry, study protocol and statistical analysis plan were used in data extraction and assessment of risk of bias. The study did not achieve the sample size recorded in the trial registry. There were no other notable differences in study population, procedures, treatments or outcomes between the published article and the trial registry, study protocol and statistical analysis plan.

Veiga TOCIBRAS 2021

Study characteristics	
Methods	RCT **Blinding:** unblinded **Date of study:** from 8 May 2020 to 17 July 2020 **Location:** multicentre (9 centres) / Brazil **Follow-up duration (days):** 29
Participants	**Population:** patients with confirmed COVID-19 (moderate-critical) **Randomised:** 129 participants (n1 tocilizumab arm = 65 / n2 control arm = 64) **Characteristics of participants** • N= 129 • Mean age: 57.4 years • 88 Males • Admitted to ICU: n = NR • Severity: mild: n = 0 / moderate: n = 67/ severe: n = 41 / critical = 21 • Patients on oxygen without intubation: n = 108 (84%); intubated: n = 21(16%) • C-reactive protein (mean): 160 to 193 mg/L **Inclusion criteria** • Confirmed diagnosis of SARS-CoV-2 infection • CT (or chest X-ray) of the chest consistent with COVID-19 • More than 3 days of symptoms related to COVID-19 • 18 years or older;

Veiga TOCIBRAS 2021 *(Continued)*

- Need for oxygen supplementation to maintain SpO_2 > 93% OR need for mechanical ventilation less than 24 hours before the randomisation
- 2 or more of the following inflammatory tests:
  - D-dimer > 1000 ng/mL;
  - C reactive protein (CRP) > 5 mg/dL;
  - ferritin > 300 mg/dL;
  - lactate dehydrogenase (LDH) > upper limit of normal.

Exclusion criteria

- Need for mechanical ventilation for 24 hours or more before the randomisation
- Hypersensitivity to tocilizumab
- Patients without therapeutic perspective or in palliative care
- Active non-controlled infections (other than COVID-19)
- Neutrophil count < 0.5 x 10^9/L
- Platelet count < 50 x 10^9/L
- Liver disease, cirrhosis or elevated AST or ALT above 5 times the upper limit of normal
- Renal disease with estimate glomerular filtration below 30 mL/min/1.72 m^2 (MDRD or CKD-EPI scores)
- Breastfeeding women
- Pregnancy
- Other clinical conditions that contraindicate tocilizumab, according to the attending physician

Dropouts and withdrawals: (0%); 0 withdrawal due to AEs

Interventions	**Intervention:** tocilizumab (8 mg/kg, IV) on day 1 up to a maximum of 800 mg. **Control:** standard care **Definition of standard care:** standard of care (best supportive care), according to the local protocol. 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. **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: 56 (86%) Standard care: 55 (86%)
Outcomes	**Primary outcome of the trial** Clinical status at 15 days evaluated with the use of a 7-level ordinal scale Note: the definition of clinical improvement extracted is discharge alive
Notes	**Funding:** mixed (the hospitals and research institutes participating in Coalition covid-19 Brazil; Fleury Laboratory (laboratory analysis); Instituto Votorantim (donation for drug provision)) **Conflict of interest:** yes, declared. "Support from hospitals and research institutes participating in the Coalition covid-19 Brazil, Fleury Laboratory in São Paulo, Brazil, and Instituto Votorantim for the submitted work. JAGGP reports support from Pfizer, Jansen, Sanofi,..." **Protocol:** yes, available. **Statistical plan:** yes, available. **Data-sharing stated:** yes, 3 months after publication. Request to the corresponding author at viviane.veiga@bp.org.br **Overall comment:** in addition to the published article and its supplementary materials, the trial registry, published protocol and statistical analysis plan were used in data extraction and 'Risk of bias' assessment. Viral clearance was an exploratory outcome in the protocol but results were not reported. There were no other substantive differences between the protocol, registry and published report in

Veiga TOCIBRAS 2021 *(Continued)*

study population, procedures or interventions. Unblinded study. The trial was terminated early after the first interim analysis owing to an excess number of deaths at 15 days in the tocilizumab group.

Quote: "The trial registration on Clinicaltrials.gov was finalised only after enrolment of the first patient because of an administrative error by the research team. Thus, the study did not achieve the sample size recorded in the trial registry. On May 8th, an eligible patient was identified at our centre and enrolment offered to the patient. At the same day, the protocol was included in ClinicalTrials.gov but could not be registered. On May 11th, we received a response with a modified Protocol Registration and Results System for registration. On May 12th, we uploaded our protocol information in ClinicalTrials.gov as approved by the Brazilian Ethics authorities. As we did not receive a reply from ClinicalTrials.gov in subsequent days, a new contact was made on May 24th and the protocol as initially submitted was published."

Quote. "In the first version of the trial protocol, need of mechanical ventilation was an exclusion criterion. On June 4th, 2020, after the study was initiated, an amendment was made to allow inclusion of patients under mechanical ventilation for less than 24 hours. On July 7th, 2020 chest X-ray evidence of COVID-19 was included as an alternative to computed tomography in the inclusion criteria"

Wang 2020

Study characteristics

Methods

RCT
Blinding: unblinded
Date of study: from 13 February 2020 to 13 March 2020
Location: multicentre / China
Follow-up duration (days): 14

Participants

Population: patients with confirmed COVID-19 (moderate-severe) to 6

Randomised: 65 participants (n1 Tocilizumab arm = 33 / n2 control arm = 32)

Characteristics of participants

- N = 65
- Mean/median age: 63 years
- 33 males
- Admitted to ICU: n = NR
- Severity: mild: n = 0 / moderate: n = 37/ severe: n = 28 / critical: n = 0
- Patients on oxygen without intubation: n = 65 (100%); Intubated: n = 0
- C-reactive protein (median): 6.28 to 9.95 mg/L

Inclusion criteria

- 18 to 85 years old
- Plasma IL-6 levels elevated
- Moderate (with bilateral pulmonary lesions) or severe in disease degree

Exclusion criteria

- Woman who is pregnant or lactating
- ALT or AST > 5 times the upper limit of normal (ULN; neutropenia < 0.5×10^9/L; platelet < 50×10^9/L;
- People diagnosed with rheumatism- and immunity-related diseases, cancer and other related diseases
- People who are taking antirejection or immunomodulatory drugs
- People who are allergic to tocilizumab or any excipients
- Patients with active hepatitis and tuberculosis, associated with specific bacterial and fungal infections

Wang 2020 *(Continued)*

	• Patients who have had organ transplantation • People with mental disorders **Dropouts and withdrawals:** 0/65 (0%); 0 withdrawal due to AEs
Interventions	**Intervention:** tocilizumab (400 mg infusion). Patients received a 2nd dose only if their condition did not improve or worsened. The number of patients received 2nd dose is not reported. **Control:** standard care **Definition of standard care:** standard care was given according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (5th or update version)". **Co-interventions** **Steroid use at baseline or any time during the study** Tocilizumab: NR Standard care: NR

Outcomes	**Primary outcome of the trial:**
	
	• Cure rate of the enrolled patients (defined as:
	  ○ fever attenuated for continuously 7 days;
	  ○ 2 times COVD-19 nucleolus acid detections negative;
	  ○ CT scan shows chest effusion absorbed more than 50% percent when the patient is discharged from hospital.

Notes	**Funding:** public/nonprofit (Department of Science and Technology of Anhui Province and Health Commission of Anhui Province, China National Center for Biotechnology Development) **Conflict of interest:** declared. No conflict of interest (quote:9 "We declare no competing interests." **Protocol:** NR **Statistical plan:** NR **Data-sharing stated:** Yes, to qualifying researchers who submit a proposal with a valuable research question. **Overall comment:** in addition to all available versions of the pre-print article, the study registry was used in data extraction and 'Risk of bias' assessment. The study did not achieve the target sample size specified in the registry. Quote: "Because of the rapid decline in the number of COVID-19 patients in China, finally a total of 65 pneumonia patients with laboratory confirmed SARS-CoV-2 infection underwent randomization." There is no change from the trial registration in the intervention and control treatments, nor in the primary outcome. Mortality was stated as a secondary outcome in the registry but not in the report. Conversely, some secondary outcomes in the report (recovery rate of hypoxia over 14 days and the time to negative virus load) were not in the registry. The study was judged to raise some concerns for 4 out of 5 domains which substantially lowered the confidence in the result, hence it was deemed an overall high risk of bias.

AE: adverse event; **ALT:** alanine aminotransferase; **AST**::aspartate aminotransferase; **CKD-EPI score:** Chronic Kidney Disease Epidemiology Collaboration; **CT:** computed tomographic; **DSMB:** Data and Safety Monitoring Board; **EU:** European Union; **ICU**: intensive care unit; **IV**: intravenous; **IL**: interleukin; **LDH**: lactate dehydrogenase; **MDRD score:** Modification of Diet in Renal Disease; **NIHR**: National Institute for Health Research; **n1:** n in experimental arm; **n2**: n in control arm; **NIV:** non-invasive ventilation; **NR**: not reported; **NYHA:** New York Heart Association; **RCT**: randomised controlled trial; **SAE**: serious adverse event;**SGOT:** Serum glutamic oxaloacetic transaminase;**SGPT;** serum glutamic pyruvic transaminase; **WHO**: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abolghasemi 2020	Not randomised or improper randomisation
Bandopadhyay 2020	Descriptive study
Behzadnia 2020	Non COVID-19 patients
Burnett 2020	Not an intervention for COVID-19
Chitra 2021	Siddha medicine
Choudhury 2021	Irrelevant intervention (gargling)
Dound 2021	Herbal medicine
Duong-Quy 2020	Irrelevant intervention (masks)
Farnoosh 2020	Irrelevant intervention
Gupta 2021	Ayurvedic medicine
Guvenmez 2020	Nebulisers without specific treatment
Huang 2020	Not randomised or improper randomisation
Hyun 2020	Not randomised or improper randomisation
Kemran 2020	Not randomised or improper randomisation
Kimura 2020	Qualitative study
Koshak 2020	Homeopathic medicine
Liu 2021	Chinese medicine
Malysz 2020	Simulation study
Mohamed 2020	Irrelevant intervention (gargling)
Mukhtar 2020	Irrelevant intervention (gargling)
Noor Azhar 2020	Simulation study
Onal 2021	Homeopathic medicine
Painter 2020	Early phase
Pizzoli 2020	Non COVID-19 patients
Saju 2020	Non COVID-19 patients
Schaller 2020	Nebulisers without specific treatment
Schumacher 2020	Simulation study
Seneviratne 2020	Irrelevant intervention (gargling)

Study	Reason for exclusion
Shapira 2021	Non COVID-19 patients
Shaw 2020	Irrelevant intervention (masks)
Simpson 2021	Irrelevant preventive intervention
Tomazini 2020	Protocol
Trieu 2021	Chinese medicine
Ward 2021	Not an intervention for COVID-19
Zhou 2020	Herbal medicine
Zhou 2021	Non COVID-19 patients

ADDITIONAL TABLES

Table 1. ROB table: tocilizumab vs standard care(SC)/placebo. Clinical improvement (D28)

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine CORIMUNO-19 2020	Low	**Some concerns[1]**	Low	**Some concerns[2]**	Low	**Some concerns**
Rosas COVACTA 2021	Low	Low	Low	Low	Low	Low
Salama EMPACTA 2020	Low	Low	Low	Low	Low	Low
Salvarani 2020	Low	**Some concerns[3]**	Low	**Some concerns[4]**	**Some concerns[5]**	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Horby RECOVERY 2021	Low	Low	Low	**Some concerns[6]**	Low	**Some concerns**
Veiga TOCIBRAS 2021	Low	**Some concerns[7]**	Low	**Some concerns[8]**	Low	**Some concerns**

[1] Quote: “Open-label study” Comment: unblinded study. Deviations from intended intervention arising because of the study context: three participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between two arms (> 10% solute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

[2] Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of clinical improvement probably does not differ between groups. Unblinded study. Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.
[3] Quote: "the trial was open label" Comment: unblinded study. Deviations from intended intervention arising because of the study context: cross over: 15 (23%) participants in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical worsening as planned in the protocol. Nevertheless, this decision could have been influenced by the trial context. Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%). These deviations could affect the outcome. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
[4] Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of clinical improvement probably does not differ between groups. Unblinded study. Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.
[5] Comment: the protocol and statistical analysis plan were available. The outcomes 'Clinical improvement (defined as discharge)' is not present in the protocol or registry. No information on whether the results for these outcomes were selected from multiple outcome measurements or analyses of the data.
[6]Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of clinical improvement probably does not differ between groups. Unblinded study. Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.
[7] Quote: “open label” trial. Comment: unblinded study. Deviations from intended intervention arising because of the study context: cross over: 2/64 (3%) of the control arm received tocilizumab. Co-interventions of interest (corticosteroids and antivirals), were reported, but no information on another co-intervention of interest: biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
[8] Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of clinical improvement probably does not differ between groups. Unblinded study. Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

Table 2. ROB table: tocilizumab vs standard care(SC)/placebo. WHO Clinical Progression Score level 7 or above (D28)

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine CORIMUNO-19 2020	Low	**Some concerns [1]**	Low	Low	Low	**Some concerns**
Rosas COVACTA 2021	Low	Low	Low	Low	Low	Low
Veiga TOCIBRAS 2021	Low	**Some concerns [2]**	Low	Low	Low	**Some concerns**

[1] Quote: “Open-label study” Comment: unblinded study.
Deviations from intended intervention arising because of the study context: three participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between two arms (>10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.
Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
[2] Quote: “open label” trial. Comment: unblinded study.
Deviations from intended intervention arising because of the study context: cross over: 2/64 (3%) of the control arm received tocilizumab. Co-interventions of interest (corticosteroids and antivirals) were reported, but no information on another co-intervention of interest: biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

Table 3. ROB table: tocilizumab vs standard care(SC)/placebo. All-cause mortality (D28)

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine CORIMUNO-19 2020	Low	**Some concerns[1]**	Low	Low	Low	**Some concerns**
Rosas COVACTA 2021	Low	Low	Low	Low	Low	Low
Salama EMPACTA 2020	Low	Low	Low	Low	Low	Low
Salvarani 2020	Low	**Some concerns[2]**	Low	Low	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Gordon REMAP-CAP 2021	Low	**Some concerns[3]**	Low	Low	Low	**Some concerns**
Horby RECOVERY 2021	Low	Low	Low	Low	Low	Low
Veiga TOCIBRAS 2021	Low	**Some concerns[4]**	Low	Low	Low	**Some concerns**

[1] Quote: “Open-label study” Comment: unblinded study.
Deviations from intended intervention arising because of the study context: three participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between two arms (> 10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
[2] Quote: "the trial was open label" Comment: unblinded study.
Deviations from intended intervention arising because of the study context: cross over: 15 (23%) participants in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical worsening as planned in the protocol. Nevertheless, this decision could have been influenced by the trial context. Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%). These deviations could affect the outcome and were not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
[3] Quote: “open-label” Comment: unblinded study.
Deviations from intended intervention arising because of the study context: no participant cross-over. Administration of co-interventions of interest: antivirals (Remdesivir, 32.8%) and corticosteroids (> 80%) were administered, but numbers per group were not reported. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
[4] Quote: “open label” trial. Comment: unblinded study.
Deviations from intended intervention arising because of the study context: cross over: 2/64 (3%) of the control arm received tocilizumab. Co-interventions of interest (corticosteroids and antivirals), were reported, but no information on another co-intervention of interest: biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Data for the outcome were analysed using intention-to-treat analysis for this outcome. This method was considered appropriate to estimate the effect of assignment to intervention.

Table 4. ROB table: tocilizumab vs standard care(SC)/placebo. All-cause mortality (≥ D60)

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine CORIMUNO-19 2020	Low	**Some concerns [1]**	Low	Low	Low	**Some concerns**
Salama EMPACTA 2020	Low	Low	Low	Low	Low	Low

[1] Quote: “Open-label study” Comment: unblinded study.
Deviations from intended intervention arising because of the study context: three participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between two arms (> 10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention

Table 5. ROB table: tocilizumab vs standard care(SC)/placebo. Incidence of any adverse events

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine CORIMUNO-19 2020	Low	**Some concerns[1]**	Low	**Some concerns[2]**	Low	**Some concerns**
Rosas COVACTA 2021	Low	Low	Low	Low	Low	Low
Salama EMPACTA 2020	Low	Low	Low	Low	Low	Low
Salvarani 2020	Low	**Some concerns[3]**	Low	**Some concerns[4]**	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Wang 2020	**Some concerns[5]**	**Some concerns[6]**	Low	**Some concerns[7]**	**Some concerns[8]**	High
Veiga TOCIBRAS 2021	Low	**Some concerns[9]**	Low	**Some concerns$_{10}$**	Low	**Some concerns**

[1] Quote: “Open-label study” Comment: unblinded study.
Deviations from intended intervention arising because of the study context: three participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between two arms (> 10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as 'Some Concerns' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.
[2] Comment: method of measuring the outcome probably appropriate. Measurement of outcome probably does not differ between groups. Unblinded study. The outcome may contain both clinically- and laboratory-detected events. Assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.
[3] Quote: "the trial was open label" Comment: unblinded study.
Deviations from intended intervention arising because of the study context: cross over: 15 (23%) participants in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical worsening as planned in the

protocol. Nevertheless, this decision could have been influenced by the trial context. Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%). These deviations could affect the outcome and were not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

[4] Comment: method of measuring the outcome probably appropriate. Measurement of outcome probably does not differ between groups. Unblinded study. The outcome may contain both clinically- and laboratory-detected events. Assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.

[5] Quote: "sation numbers were generated using SAS statistical software package (SAS Institute, Cary, USA). A computer- generated 1:1 block randomization scheme was used to assign participants to either treatment group or control one. Each consecutively coded participant was randomly enrolled by the sub-site investigators until the total number of cases allocated to the site was reached." Comment: Allocation sequence random. Allocation concealment unclear.

[6] Quote: "One case in the control group aggravated on day three after randomization was transferred to the tocilizumab group according to the rules of the study protocol." Comment: unblinded study. Deviations from intended intervention arising because of the study context: one participant cross-over. No information on administration of any co-interventions of interest: antivirals, corticosteroids, biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Participants were not analysed according to their randomised groups for the outcome. Of note, 1 participant randomised to the control group was analysed in the intervention group. Nevertheless, we considered the analysis to be probably appropriate to estimate the effect of assignment to intervention.

[7] Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study. The outcome contains both clinically- and laboratory-detected events. Assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.

[8] Comment: the protocol and statistical analysis plan were not available. The registry was available. Adverse events were not mentioned in the registry but reported in the paper. No information on whether results were selected from multiple outcome measurements or analyses of the data.

9 Quote: “open label” trial. Comment: unblinded study.
Deviations from intended intervention arising because of the study context: cross over: 2/64 (3%) of the control arm received tocilizumab. Co-interventions of interest (corticosteroids and antivirals) were reported, but no information on another co-intervention of interest: biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported.
Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

[10] Comment: method of measuring the outcome probably appropriate. Measurement of outcome probably does not differ between groups. Unblinded study. The outcome contains both clinically- and laboratory-detected events. Assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.

Table 6. ROB table: tocilizumab vs standard care(SC)/placebo. Incidence of serious adverse events

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine CORIMUNO-19 2020	Low	**Some concerns [1]**	Low	**Some concerns [2]**	Low	**Some concerns**
Rosas COVACTA 2021	Low	Low	Low	Low	Low	Low
Salama EMPACTA 2020	Low	Low	Low	Low	Low	Low
Salvarani 2020	Low	**Some concerns[3]**	Low	**Some concerns[4]**	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Wang 2020	**Some concerns [5]**	**Some concerns [6]**	Low	**Some concerns [7]**	**Some concerns[8]**	High

Table 6. ROB table: tocilizumab vs standard care(SC)/placebo. Incidence of serious adverse events *(Continued)*

Gordon REMAP-CAP 2021	Low	**Some concerns [9]**	Low	**Some concerns[10]**	Low	**Some concerns**
Veiga TOCIBRAS 2021	Low	**Some concerns[11]**	Low	**Some concerns [12]**	Low	**Some concerns**

[1] Quote: “Open-label study” Comment: unblinded study.
Deviations from intended intervention arising because of the study context: three participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between two arms (> 10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

[2] Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study. The outcome contains both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

[3] Quote: "the trial was open label" Comment: unblinded study.
Deviations from intended intervention arising because of the study context: Cross over: 15 (23%) participants in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical worsening as planned in the protocol. Nevertheless, this decision could have been influenced by the trial context. Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%). These deviations could affect the outcome and were not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

[4] Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study. The outcome contains both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

[5] Quote: "Randomization numbers were generated using SAS statistical software package (SAS Institute, Cary, USA). A computer- generated 1:1 block randomization scheme was used to assign participants to either treatment group or control one. Each consecutively coded participant was randomly enrolled by the sub-site investigators until the total number of cases allocated to the site was reached." Comment: allocation sequence random. Allocation concealment unclear.

[6] Quote: "One case in the control group aggravated on day three after randomization was transferred to the tocilizumab group according to the rules of the study protocol." Comment: unblinded study. Deviations from intended intervention arising because of the study context: One participant cross-over. No information on administration of any co-interventions of interest: antivirals, corticosteroids, biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Participants were not analysed according to their randomised groups for the outcome. Of note, 1 participant randomised to the control group was analysed in the intervention group. Nevertheless, we considered the analysis to be probably appropriate to estimate the effect of assignment to intervention.

[7] Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study. The outcome may contain both clinically- and laboratory-detected events. Assessment of this outcome can be influenced by knowledge of the intervention assignment but is not likely in the context of a pandemic.

[8] The protocol and statistical analysis plan were not available. The registry was available. Serious adverse events were not mentioned in the registry but reported in the paper. No information on whether results were selected from multiple outcome measurements or analyses of the data.

[9] Quote: “open-label” Comment: unblinded study. Deviations from intended intervention arising because of the study context: No participant cross-over. Administration of co-interventions of interest: antivirals (Remdesivir, 32.8%) and corticosteroids (> 80%) were administered, but numbers per group were not reported. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

[10] Comment: method of measuring outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor). Outcome may contain both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

[11] Quote: “open label” trial. Comment: unblinded study.
Deviations from intended intervention arising because of the study context: Cross over: 2/64 (3%) of the control arm received tocilizumab. Co-interventions of interest (corticosteroids and antivirals), were reported, but no information on another co-intervention of interest: biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

[12] Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study. The outcome contains both clinically- and laboratory-detected events which can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic

Table 7. ROB table: tocilizumab vs standard care(SC)/placebo. Time to clinical improvement

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Gordon REMAP-CAP 2021	Low	**Some concerns[1]**	Low	**Some concerns[2]**	Low	**Some concerns**
Hermine CORIMUNO-19 2020	Low	**Some concerns[3]**	Low	**Some concerns[4]**	Low	**Some concerns**
Rosas COVACTA 2021	Low	Low	Low	Low	Low	Low
Salama EMPACTA 2020	Low	**Some concerns[5]**	Low	Low	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Salvarani 2020	Low	**Some concerns[6]**	Low	**Some concerns[7]**	**Some concerns[8]**	**Some concerns**

[1] Quote: “open-label” Comment: unblinded study. Deviations from intended intervention arising because of the study context: No participant cross-over. Administration of co-interventions of interest: antivirals (Remdesivir, 32.8%) and corticosteroids (> 80%) were administered, but numbers per group were not reported. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Participants were analysed according to their randomised groups for the outcome. Of note, 13 vs 10 participants were excluded from the analysis post-randomisation for reasons related to missing data. This method was considered appropriate to estimate the effect of assignment to intervention.

[2] Comment: method of measuring outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor). Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

[3] Quote: “Open-label study” Comment: unblinded study.

Deviations from intended intervention arising because of the study context: three participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between two arms (> 10% absolute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as 'Some Concerns' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect.

Participants were analysed according to their randomized groups for the outcome. Of note, 1 vs 0 participants were excluded from the analysis because of consent withdrawal. Nevertheless, we consider the analysis appropriate to estimate the effect of assignment to intervention.

[4] Comment: method of measuring the outcome probably appropriate.

Measurement or ascertainment of outcome probably does not differ between groups Unblinded study. Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

[5] Quote: “double-blind, placebo-controlled trial.” “A site blinding plan was established at each site to identify which personnel would be blinded or unblinded at a site level. A pharmacy manual and specific training in addition to completion of a site blinding plan was provided to each site. Each site had an unblinded pharmacist that randomized the participant and prepared and labeled study medication in the same method for both tocilizumab and placebo. The remainder of the study team was blinded to treatment assignment. There was no communication during the study between unblinded and blinded members. In addition, there was an unblinded medical monitor available to answer questions from the unblinded site staff. Placebo was not provided and consisted of an unaltered saline infusion bag, the same as would be used to prepare tocilizumab. The volume of tocilizumab diluted in saline appears colorless and matches saline.” Comment: blinded study. Participants were blinded. Carers were probably blinded.

Participants were analysed according to their randomised groups for the outcome. Of note, 10 vs 1 participants were excluded from the analysis post-randomisation because they did not receive the drug. This method was considered inappropriate to estimate the effect of

assignment to intervention for this time-to-event outcome. There was probably no substantial impact of failure to analyse participants according to their randomised groups.

[6] Quote: "the trial was open label" Comment: unblinded study.
Deviations from intended intervention arising because of the study context: cross over: 15 (23%) participants in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical worsening as planned in the protocol. Nevertheless, this decision could have been influenced by the trial context. Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%). These deviations could affect the outcome and were not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analyced using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

[7] Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups Unblinded study. Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

[8] Comment: the protocol and statistical analysis plan were available. The outcome time to clinical improvement (defined as time to discharge) is not mentioned in the protocol or registry. No information on whether the results for these outcomes were selected from multiple outcome measurements or analyses of the data.

Table 8. ROB table: tocilizumab vs standard care(SC)/placebo. Time to WHO score 7 or above

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Hermine CORIMUNO-19 2020	Low	**Some concerns [1]**	Low	Low	Low	**Some concerns**
Salama EMPACTA 2020	Low	**Some concerns [2]**	Low	Low	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low

[1] Quote: “Open-label study” Comment: unblinded study.
Deviations from intended intervention arising because of the study context: 3 participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between 2 arms (> 10% absolute difference between the 2 arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as Some Concerns as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Participants were analysed according to their randomised groups for the outcome. Of note, 1 vs 0 participants were excluded from the analysis because of consent withdrawal. Nevertheless, we consider the analysis appropriate to estimate the effect of assignment to intervention.

[2] Quote: “double-blind, placebo-controlled trial.” “A site blinding plan was established at each site to identify which personnel would be blinded or unblinded at a site level. A pharmacy manual and specific training in addition to completion of a site blinding plan was provided to each site. Each site had an unblinded pharmacist that randomized the participant and prepared and labeled study medication in the same method for both tocilizumab and placebo. The remainder of the study team was blinded to treatment assignment. There was no communication during the study between unblinded and blinded members. In addition, there was an unblinded medical monitor available to answer questions from the unblinded site staff. Placebo was not provided and consisted of an unaltered saline infusion bag, the same as would be used to prepare tocilizumab. The volume of tocilizumab diluted in saline appears colorless and matches saline.”
Comment: Blinded study. Participants were blinded. Carers were probably blinded. Participants were analysed according to their randomised groups for the outcome. Of note, 10 vs 1 participants were excluded from the analysis post-randomisation because they did not receive the drug. This method was considered inappropriate to estimate the effect of assignment to intervention for this time-to-event outcome. There was probably no substantial impact of failure to analyse participants according to their randomised groups

Table 9. ROB table: tocilizumab vs standard care(SC)/placebo. Time to death

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement	5.Selection of the	Overall risk of bias

Table 9. ROB table: tocilizumab vs standard care(SC)/placebo. Time to death *(Continued)*

				of the outcome	reported results	
Gordon REMAP-CAP 2021	Low	**Some concerns [1]**	Low	Low	Low	**Some concerns**
Hermine CORIMUNO-19 2020	Low	**Some concerns [2]**	Low	Low	Low	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low

[1] Quote: "open-label" Comment: unblinded study. Deviations from intended intervention arising because of the study context: No participant cross-over. Administration of co-interventions of interest: antivirals (Remdesivir, 32.8%) and corticosteroids (> 80%) were administered, but numbers per group were not reported. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Participants were analysed according to their randomised groups for the outcome. Of note, 13 vs 10 participants were excluded from the analysis post-randomisation for reasons related to missing data. This method was considered appropriate to estimate the effect of assignment to intervention.
[2] Quote: "Open-label study" Comment: unblinded study.
Deviations from intended intervention arising because of the study context: three participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between 2 arms (> 10% absolute difference between the 2 arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as Some Concerns as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Participants were analysed according to their randomised groups for the outcome. Of note, 1 vs 0 participants were excluded from the analysis because of consent withdrawal. Nevertheless, we consider the analysis appropriate to estimate the effect of assignment to intervention.

Table 10. ROB table: sarilumab vs standard care(SC). All-cause mortality (D28)

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Gordon REMAP-CAP 2021	Low	**Some concerns [1]**	Low	Low	Low	**Some concerns**
Lescure 2021	Low	Low	Low	Low	Low	Low

[1] Quote: "open-label" Comment: unblinded study. Deviations from intended intervention arising because of the study context: No participant cross-over. Administration of co-interventions of interest: antivirals (Remdesivir, 32.8%) and corticosteroids (> 80%) were administered, but numbers per group were not reported. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Participants were analysed according to their randomised groups for the outcome. Of note, 3 vs 15 participants were excluded from the analysis post-randomisation for reasons related to missing data. This method was considered appropriate to estimate the effect of assignment to intervention.

Table 11. ROB table: sarilumab vs standard care(SC). All-cause mortality (≥ D60)

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lescure 2021	Low	Low	Low	Low	**Some concerns [1]**	**Some concerns**

[1] Comment: the study registry was available. Mortality outcome was not pre-specified for day 60 in the registry. No information whether the result was selected from multiple outcome measurements or analyses of the data.

Table 12. ROB table: sarilumab vs standard care(SC). Incidence of adverse events

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Lescure 2021	Low	Low	Low	Low	Low	Low

Table 13. ROB table: sarilumab vs standard care(SC). Incidence of serious adverse events

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Gordon REMAP-CAP 2021	Low	**Some concerns [1]**	Low	**Some concerns [2]**	Low	**Some concerns**
Lescure 2021	Low	Low	Low	Low	Low	Low

[1] Quote: "open-label" Comment: unblinded study. Deviations from intended intervention arising because of the study context: No participant cross-over. Administration of co-interventions of interest: antivirals (Remdesivir, 32.8%) and corticosteroids (> 80%) were administered, but numbers per group were not reported. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Participants were analysed according to their randomised groups for the outcome. Of note, 3 vs 10 participants were excluded from the analysis post-randomisation for reasons related to missing data. This method was considered appropriate to estimate the effect of assignment to intervention.
[2] Comment: method of measuring outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor). Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

Table 14. ROB table: sarilumab vs standard care(SC). Time to clinical improvement

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Gordon REMAP-CAP 2021	Low	**Some concerns [1]**	Low	**Some concerns[2]**	Low	**Some concerns**
Lescure 2021	Low	Low	Low	Low	Low	Low

[1] Quote: "open-label" Comment: unblinded study. Deviations from intended intervention arising because of the study context: No participant cross-over. Administration of co-interventions of interest: antivirals (Remdesivir, 32.8%) and corticosteroids (> 80%) were administered, but numbers per group were not reported. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Participants were analysed according to their randomised groups for the outcome. Of note, 3 vs 10 participants were excluded from the analysis post-randomisation for reasons related to missing data. This method was considered appropriate to estimate the effect of assignment to intervention.
[2] Comment: method of measuring outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Unblinded study (outcome assessor). Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

Table 15. ROB table: sarilumab vs standard care(SC). Time to death

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias
Gordon REMAP-CAP 2021	Low	**Some concerns**[1]	Low	Low	Low	**Some concerns**

[1] Quote: "open-label" Comment: unblinded study. Deviations from intended intervention arising because of the study context: No participant cross-over. Administration of co-interventions of interest: antivirals (Remdesivir, 32.8%) and corticosteroids (> 80%) were administered, but numbers per group were not reported. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Participants were analysed according to their randomised groups for the outcome. Of note, 3 vs 10 participants were excluded from the analysis post-randomisation for reasons related to missing data. This method was considered appropriate to estimate the effect of assignment to intervention

APPENDICES

Appendix 1. Living process of the review

Steering committee

We set up a steering committee of epidemiologists, methodologists, statisticians and clinicians with content expertise. This committee will meet regularly, discuss the conduct of the project, difficulties encountered and possible changes in the protocol according to new knowledge available on COVID-19 disease. Changes in the protocol could consist for example of changes in the search strategy, eligibility criteria (e.g. study design), research questions for the pairwise meta-analyses, outcomes.

Process and quality control

Our aim is to update the synthesis at least every week. For this purpose, we will search, screen and extract data every day. The updated synthesis will be reported online at least every week.

To standardise the process and ensure both rapidity and quality, we will proceed as follows.

1. We will separate the process into different tasks and set up a team for each task (i.e. a researcher/volunteer will be involved in a single task). Each team will be led by a senior researcher ensuring the quality and standardisation of the task.
2. For some tasks, we will develop a short training program for researchers/volunteers joining the team. This program will involve:
   a. reading a manual detailing the task;
   b. performing the task on a sample as an exercise (e.g. evaluating the risk of bias of three studies) and contacting the team leader to ask about difficulties; and
   c. after a successful training, the newcomer will perform the double data extraction with a senior well-trained researcher.
3. Each team will hold a weekly meeting to discuss difficulties and ensure standardization. All decisions and changes will be recorded.
4. We will set-up an internal quality control process where a senior researcher, and former editor in chief of Cochrane, (D Tovey) will check the data extracted and reported on the website. All points will be discussed with the data extraction team and modifications recorded for transparency.
5. We will develop an external quality control process for data collection involving senior researchers who will check a random sample of the data collected (e.g. member of the Cochrane Bias Methods Group for risk of bias)

We will consider the following tasks:

1. research mapping: screening and extracting data from registries;
2. screening of databases from title/abstract to full text;
3. data extraction;
4. data analyses;
5. assessment of evidence certainty.

The core team will perform the analysis, presentation and interpretation of the results.

Evolution of the protocol over time

The process will also evolve over time according to the new knowledge available regarding COVID-19.

The steering committee will systematically discuss and achieve consensus on the changes of protocol proposed.

Appendix 2. Case definitions

Suspect case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g. cough, shortness of breath)), AND with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 disease during the 14 days prior to symptom onset.

OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days before onset of symptoms.

OR

C. A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g. cough, shortness breath)) AND requiring hospitalisation AND no other etiology that fully explains the clinical presentation.

Probable case

A suspect case for whom testing for COVID-19 is inconclusive (inconclusive being the result of the test reported by the laboratory).

Confirmed case

A person with laboratory confirmation of COVID-19 infection, regardless of clinical signs and symptoms.

Of note, when the definition used to classify cases was not clearly reported, we will rely on the classification provided by authors.

Appendix 3. Search strategies

Current Strategy (last updated 11 December 2020)

Source
PubMed
(2019 nCoV[tiab] OR 2019nCoV[tiab] OR corona virus[tiab] OR corona viruses[tiab] OR coronavirus[tiab] OR coronaviruses[tiab] OR COVID[tiab] OR COVID19[tiab] OR nCov 2019[tiab] OR SARS-CoV2[tiab] OR SARS CoV-2[tiab] OR SARSCoV2[tiab] OR SARSCoV-2[tiab] OR "COVID-19"[Mesh] OR "COVID-19 Testing"[Mesh] OR "COVID-19 Vaccines"[Mesh] OR "Coronavirus"[Mesh:NoExp] OR "SARS-CoV-2"[Mesh] OR "COVID-19"[nm] OR "COVID-19 drug treatment"[nm] OR "COVID-19 diagnostic testing"[nm] OR "COVID-19 serotherapy"[nm] OR "COVID-19 vaccine"[nm] OR "LAMP assay"[nm] OR "severe acute respiratory syndrome coronavirus 2"[nm] OR "spike protein, SARS-CoV-2"[nm]) NOT ("animals"[mh] NOT "humans"[mh]) NOT (editorial[pt] OR newspaper article[pt])
Embase.com
((('coronaviridae'/de OR 'coronavirinae'/de OR 'coronaviridae infection'/de OR 'coronavirus disease 2019'/exp OR 'coronavirus infection'/de OR 'SARS-related coronavirus'/de OR 'Severe acute respiratory syndrome coronavirus 2'/exp OR '2019 nCoV':ti,ab,kw OR 2019nCoV:ti,ab,kw OR ((corona* OR corono*) NEAR/1 (virus* OR viral* OR virinae*)):ti,ab,kw OR coronavir*:ti,ab,kw OR coronovir*:ti,ab,kw OR COVID:ti,ab,kw OR COVID19:ti,ab,kw OR HCoV*:ti,ab,kw OR 'nCov 2019':ti,ab,kw OR 'SARS CoV2':ti,ab,kw OR 'SARS CoV 2':ti,ab,kw OR SARSCoV2:ti,ab,kw OR 'SARSCoV 2':ti,ab,kw) NOT (('animal experiment'/de OR 'animal'/exp) NOT ('human'/exp OR 'human experiment'/de))) NOT 'editorial'/it) NOT ([medline]/lim OR [pubmed-not-medline]/lim) AND [1-12-2019]/sd
CENTRAL

(Continued)

1 ("2019 nCoV" OR 2019nCoV OR "corona virus*" OR coronavirus* OR COVID OR COVID19 OR "nCov 2019" OR "SARS-CoV2" OR "SARS CoV-2" OR SARSCoV2 OR "SARSCoV-2"):TI,AB AND CENTRAL:TARGET

2 Coronavirus:MH AND CENTRAL:TARGET

3 Coronavirus:EH AND CENTRAL:TARGET

4 #1 OR #2 OR #3

5 2019 TO 2021:YR AND CENTRAL:TARGET

6 #5 AND #4

7 INSEGMENT

8 #6 NOT #7

ClinicalTrials.gov

COVID-19 OR 2019-nCoV OR SARS-CoV-2 OR coronavirus

WHO ICTRP

We screen the entire COVID-19.csv file available from https://www.who.int/emergencies/diseases/novel-coronavirus-2019

medRxiv

We screen the entire COVID-19 results identified by the Stephen B. Thacker CDC Library

LOVE

Source	Search strategy
Epistemonikos Database	coronavir* OR coronovirus* OR betacoronavir* OR "beta-coronavirus" OR "beta-coronaviruses" OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR "covid-19" OR covid19* OR "covid 19" OR "2019-ncov" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR (wuhan* and (virus OR viruses OR viral)) OR sars* OR sari OR (covid* and (virus OR viruses OR viral)) OR "severe acute respiratory syndrome" OR mers* OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome" OR "covid-19-related" OR "2019-ncov-related" OR "cv-19-related" OR "n-cov-related"

Appendix 4. Characteristics of registered studies

Characteristics of unpublished studies: completed studies

NCT04315298	
Trial name or title	Evaluation of the efficacy and safety of sarilumab in hospitalized patients With COVID-19
Methods	RCT, placebo-controlled, double-blind study Date of study: March 2020 Location: USA

(Continued)

	Phase 2/3

Participants	Randomised: 1912 participants
	
	Inclusion criteria
	
	• Laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR), result from any specimen (or other commercial or public health assay) within 2 weeks prior to randomisation and no alternative explanation for current clinical condition
	• Hospitalised with illness of any duration with evidence of pneumonia, requires supplemental oxygen and/or assisted ventilation and meets one of the following:
	• Phase 2 and phase 3 cohort 1: meets 1 of the following criteria at baseline:
	  • severe disease or
	  • critical disease or
	  • multi-system organ dysfunction or
	  • immunocompromised
	• Phase 3 cohort 2: patients must be receiving mechanical ventilation to treat respiratory failure due to COVID-19:
	  • ability to provide informed consent signed by study patient or legally acceptable representative
	  • willingness and ability to comply with study-related procedures/assessments
	
	Exclusion criteria
	
	• In the opinion of the investigator, not expected to survive for more than 48 hours from screening
	• Presence of any of the following abnormal laboratory values at screening:
	  ◦ absolute neutrophil count (ANC) less than 2000 mm^3;
	  ◦ aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN);
	  ◦ platelets <50,000 per mm^3.
	• Treatment with anti-IL 6, anti-IL-6R antagonists, or with Janus kinase inhibitors (JAKi) in the past 30 days or plans to receive during the study period
	• Current treatment with the simultaneous combination of leflunomide and methotrexate
	• Known active tuberculosis (TB), history of incompletely treated TB, suspected or known extrapulmonary TB, suspected or known systemic bacterial or fungal infections
	• Participation in a double-blind clinical research study evaluating an investigational product (IP) or therapy within 3 months and less than 5 half-lives of IP prior to the screening visit. (The use of remdesivir, hydroxychloroquine, or other treatments being used for COVID-19 treatments in the context of an open-label study, emergency use authorisation (EUA), compassionate use protocol or open-label use is permitted)
	• Any physical examination findings, and/or history of any illness, concomitant medications or recent live vaccines that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study
	• Known systemic hypersensitivity to sarilumab or the excipients of the drug product
	
	Phase 3 cohort 2 only
	
	• Known or suspected history of immunosuppression or immunodeficiency disorder
	• Patients who require renal replacement therapy for acute kidney injury at randomisation or who required renal replacement therapy within 72 hours prior to randomisation
	• Patients who have circulatory shock requiring vasopressors at randomisation or within 24 hours prior to randomisation
	• Use of extracorporeal life support (e.g. ECMO) or, in the opinion of the investigator, there is a high likelihood that extracorporeal life support will be initiated within 48 hours after randomisation

Interventions	**Intervention:** sarilumab (low, mild or high dose, dosage not stated)

(Continued)

	Control interventions: placebo
Outcomes	**Primary outcome** • Proportion of patients with at least 1-point improvement in clinical status (day 4) **Secondary outcomes** • Time to improvement (up to day 29) • Number of patients requiring initiation of mechanical ventilation (up to day 29) • Number of patients requiring non-invasive ventilation • Number of deaths (up to day 29)
Starting date	Study start date: 18 March 2020 Study completion date: 2 September 2020
Contact information	Regeneron Pharmaceuticals
Notes	Completed

EUCTR-2020-001162-12-FR	
Trial name or title	An adaptive phase 3, randomized, double-blind, placebo-controlled, study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19
Methods	RCT, placebo-controlled, double-blind study Date of study: March 2020 Location: Canada, France, Germany, Israel, Italy, Japan, Russian Federation, Spain Phase 2/3
Participants	Randomised: 460 participants **Inclusion criteria** • Severe disease • Multisystem organ dysfunction or critical disease • Laboratory-confirmed SARS-CoV-2 infection **Exclusion criteria** • Unlikely to survive for > 48 hours from screening • Presence of neutropenia less than 2000/mmˆ3, AST or ALT greater than 5 X ULN, platelets less than 50,000/mmˆ3 • Prior immunosuppressive therapies • Use of chronic oral corticosteroids for non-COVID-19 related condition • Past or current history of autoimmune or inflammatory disease(s) • Known or suspected history of tuberculosis • Suspected or known active systemic bacterial or fungal infections
Interventions	**Intervention:** sarilumab (IV, 200 mg)

(Continued)

	Control interventions: placebo (IV)
Outcomes	**Primary outcome** **Secondary outcomes** • Time to clinical improvement • Change in 7-point ordinal scale (baseline to days 3, 5, 8, 11,15, and 29) • Clinical status using the 7-point ordinal scale • Mortality (baseline to day 60) • Adverse events (baseline to day 60)
Starting date	Study start date: 26 March 2020 Study completion date: 29 September 2020
Contact information	Sanofi-Aventis France, Public-Registry-MA-France@sanofi.com
Notes	Completed

NCT04380519	
Trial name or title	Study of the efficacy and safety of a single administration of olokizumab and RPH-104 with standard therapy in patients with severe severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)
Methods	RCT, placebo-controlled, double-blind study Date of study: May 2020 Location: Russian Federation Phase 2/3
Participants	Randomised: 372 participants **Inclusion criteria** • Signed and dated patient's Informed consent for participation in this study, or record of a medical board decision justifying patient's participation in case of patient is unable to state his/her will. • Having either of the following COVID-associated respiratory syndromes: • ○ pneumonia with oxygenation parameters $SpO_2 \leq 93\%$ (on room air) or respiratory rate greater than 30/min; ○ ARDS ($PaO_2/FiO_2 \leq 300$ mmHg or $SpO_2/FiO_2 \leq 315$ if PaO_2 is not available). • COVID-19 diagnosis based on: • laboratory-confirmed SARS-CoV-2 infection as determined by PCR method; or • bilateral changes in the lungs typical for COVID-19, based on chest computed tomography results. **Exclusion criteria** • Hypersensitivity to the study drugs (RPH-104 and/or OKZ), and/or its components • Presence of any of the following laboratory abnormalities: • absolute neutrophil counts < 0.5 x 10^9 L • white blood cell count < 2 x 10^9 L

(Continued)

	• platelet count < 50 x 10^9 L • ALT and/or AST ≥ 3.0 x ULN • Severe renal failure: creatinine clearance < 30 mL/min • Septic shock (to maintain mean arterial pressure ≥ 65 mm Hg and lactate ≥ 2 mmol/L in the absence of hypovolaemia, vasopressors are necessary) • Progression of disease up to the death in the following 24 hours regardless of treatment, as per Investigator's opinion • History of perforation of gastrointestinal tract, history of diverticulitis • Plasma infusion from convalescent COVID-19 donors within 4 weeks prior to patient inclusion and/or planned infusion during the study • Recent (less then 5 half-lives) administration of tocilizumab or sarilumab; • Recent (less then 5 half-lives) or planned during the current study period use of the following drugs: ◦ immunosuppressive biologics over than OKZ or RPH-104, including but not limited, Interleukin-1 (IL-1) inhibitors (rilonacept, anakinra, canakinumab), IL-6 inhibitors (except tocilizumab and sarilumab), IL-17A inhibitors (secukinumab), tumour necrosis factor α (TNFα) inhibitors (adalimumab, infliximab, etanercept), anti-B-cell therapy and others ◦ other immunosuppressors except methotrexate dosed up to 25 mg per week, including but not limited: ■ high-dose glucocorticoids (> 1 mg/kg of prednisolone equivalent), oral and parental; ■ JAK inhibitors, cyclophosphamide, and others • Concurrent participation in another clinical trial • Pregnancy or lactation • History of active tuberculosis, active tuberculosis suspected by Investigator
Interventions	**Intervention** • RPH-104 (SC, 80 mg, single injection) • Olokizumab (SC, 64 mg, single injection) **Control interventions** • Placebo
Outcomes	**Primary outcome** **Secondary outcomes** • Changes of patients' clinical status on a 6 points ordinal scale (day 2 until day 15, day 29) • Mortality (day 1 until day 29) • Time to clinical improvement of clinical status (day 1 until day 29)
Starting date	Study start date: 23 April 2020 Study completion date: 24 July 2020
Contact information	R-Pharm, Mikhail Samsonov
Notes	Completed

NCT04397562	
Trial name or title	A clinical trial of the efficacy and safety of levilimab (BCD-089) in patients with severe COVID-19

(Continued)

Methods	RCT, placebo-controlled, double-blind study Date of study: May 2020 Location: Russian Federation Phase 3

Participants	Randomised: 206 participants
	
	Inclusion criteria
	
	• Signed informed consent (participant; legally authorised representative) or signed conclusion of panel of independent medical doctors
	• Males and non-pregnant females aged 18 years or older at the IC date
	• Positive test for SARS-CoV2 nucleic acid (RNA) at the IC date
	• Admitted as inpatient to a hospital with radiologically-confirmed pneumonia
	• Severe form of COVID-19.
	• Participants meeting any of the following criteria:
	  • total respiratory rate > 30 breaths per minute;
	  • $SpO_2 \leq 93\%$;
	  • $PaO_2 / FiO_2 \leq 300$ mmHg;
	  • chest imaging (X-ray, CT, US) showed lesion progression within 24 to 48 hours > 50%;
	  • decrease of consciousness level, psychomotor agitation/irritability
	  • haemodynamically unstable (systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg or urine output < 20 mL/hour)
	  • arterial lactate > 2 mmol/L;
	  • qSOFA (quick sequential organ failure assessment score) > 2. Participants meeting 3 following criteria:
	  ○ low blood pressure (SBP ≤ 100 mmHg);
	  ○ high respiratory rate (≥ 22 breaths/min);
	  ○ altered mentation (Glasgow Coma Scale ≤ 14).
	
	Exclusion criteria
	
	• Critical COVID-19. Participants meeting any of the following:
	  ○ respiratory failure and requiring invasive mechanical ventilation (tracheal intubation);
	  ○ septic shock;
	  ○ multiple organ failure;
	  ○ life expectancy < 24 hours in the opinion of the investigator;
	  ○ unlikely to remain at the investigational site beyond 48 hours;
	  ○ use of other monoclonal antibodies for COVID-19 treatment;
	  ○ current treatment with immunosuppressive agents (including corticosteroids);
	  ○ participating in other drug clinical trials at the IC date or within 60 days after randomisation (participation in COVID-19 anti-viral trials may be permitted if approved by Sponsor).
	• Laboratory values:
	• ○ ALT / AST > 10 ULN at screening
	  ○ platelets < 50 x 109/L at screening
	  ○ absolute neutrophil count < 1 x 109/L at screening
	  ○ suspected active bacterial, fungal, viral, or other infection (besides COVID-19)
	  ○ confirmed active TB
	  ○ history of allergic reaction to monoclonal antibodies
	• Pregnancy or breastfeeding
	• Any illness or laboratory findings that, in the opinion of the study investigator, might pose an additional risk to the patient by their participation in the study

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Interventions	**Intervention: l**evilimab (SC, 324 mg) **Control interventions:** standard of care
Outcomes	**Primary outcome** **Secondary outcomes** • Patients reporting each category of 7-Category Ordinal Scale of Clinical Status (day 30) • Proportion of patients transferred to the ICU (day 60)
Starting date	Study start date: 29 April 2020 Study completion date: 3 August 2020
Contact information	Biocad
Notes	Completed

NCT04479358	
Trial name or title	Low-dose tocilizumab versus standard of care in hospitalized patients with COVID-19
Methods	RCT, active-controlled, open-label study Date of study: July 2020 Location: USA Phase 2
Participants	Randomised: 332 participants **Inclusion criteria** • Adults ≥ 18 years of age • Approval from the patient's primary inpatient service • Hospitalised • Fever, documented in electronic medical record and defined as: T ≥ 38 degrees C by any conventional clinical method (forehead, tympanic, oral, axillary, rectal) • Positive test for active SARS-CoV-2 infection • Radiographic evidence of infiltrates on chest radiograph (CXR) or computed tomography (CT) • Ability to provide written informed consent on the part of the participant or, in the absence of decisional capacity of the participant, an appropriate surrogate (e.g. a legally authorised representative). **Exclusion criteria** • Concurrent use of invasive mechanical ventilation • Concurrent use of vasopressor or inotropic medications • Previous receipt of tocilizumab or another anti-IL6R or IL-6 inhibitor in the year prior • Known history of hypersensitivity to tocilizumab • Diagnosis of end-stage liver disease or listed for liver transplant. • Elevation of AST or ALT in excess of 10 times the upper limit of normal • Neutropenia (absolute neutrophil count < 500/uL)

(Continued)

	• Thrombocytopenia (platelets < 50,000/uL).
	• On active therapy with a Bruton's tyrosine kinase-targeted agent, which include the following:
	  ○ acalabrutinib;
	  ○ ibrutinib;
	  ○ zanubrutinib.
	• On active therapy with a JAK2-targeted agent, which include the following: tofacitinib, baricitinib, upadacitinib, ruxolitinib
	• Any of the following biologic immunosuppressive agent (and any biosimilar versions thereof) administered in the past 6 months or less: abatacept, adalimumab, alemtuzumab, atezolizumab, belimumab, blinatumomab, brentuximab, certolizumab, daratumumab, durvalumab, eculizumab, elotuzumab, etanercept, gemtuzumab, golimumab, ibritumomab, infliximab, inotuzumab, ipilimumab, ixekizumab, moxetumomab, nivolumab, obinutuzumab, ocrelizumab, ofatumumab, pembrolizumab, polatuzumab, rituximab, rituximab, sarilumab, secukinumab, tocilizumab, tositumumab, tremelimumab, urelumab, ustekinumab
	• History of bone marrow transplantation (including chimeric antigen receptor T-cell) or solid organ transplant
	• Known history of Hepatitis B or Hepatitis C (patients who have completed curative-intent anti-HCV treatments are not excluded from trial)
	• Positive result on hepatitis B or C screening
	• Known history of mycobacterium tuberculosis infection at risk for reactivation
	• Known history of gastrointestinal perforation
	• Active diverticulitis
	• Multi-organ failure as determined by primary treating physicians
	• Any other documented serious, active infection besides COVID-19 - including but not limited to: lobar pneumonia consistent with bacterial infection, bacteraemia, culture-negative endocarditis, or current mycobacterial infection - at the discretion of primary treating physicians
	• Pregnant patients or nursing mothers
	• Patients who are unable to discontinue scheduled antipyretic medications, either as monotherapy (e.g. acetaminophen or ibuprofen (aspirin is acceptable)) or as part of combination therapy (e.g. hydrocodone/acetaminophen, aspirin/acetaminophen/caffeine [Excedrin®])
	• CRP < 40 mg/L

Interventions	**Intervention:** ·tocilizumab (IV, 8 mg/kg, up to a maximum dose 800 mg, up to 1 additional dose may be given if clinical symptoms worsen or show no improvement) **Control interventions:** placebo
Outcomes	**Primary outcome** **Secondary outcomes** • Mortality (28 days) • Time to non-elective invasive mechanical ventilation (up to day 28) • Adverse events (28 days)
Starting date	Study start date: 10 September 2020
Contact information	University of Chicago Medicine, Pankti D Reid, pankti.reid@uchospitals.edu
Notes	Completed

IRCT20200525047570N1

(Continued)

Trial name or title	A comparative study of the effects of tocilizumab, interferon-gamma and vitamin C on the recovery of critically ill Covid-19 patients and cytokine storm
Methods	RCT, active-controlled, open-label study Date of study: July 2020 Location: Iran Phase 2
Participants	Randomised: 60 participants **Inclusion criteria** • Lack of a specific clinical disease • Non-use of a particular drug • No pregnancy **Exclusion criteria** • A specific clinical disease • Taking a particular drug • Pregnancy
Interventions	**Intervention**: tocilizumab (SC, 62 mg/0.9 mL, 1 time a week for 2 weeks) **Control interventions**: standard of care
Outcomes	**Primary outcome** **Secondary outcomes**
Starting date	Study start date:-
Contact information	Tabriz University of Medical Sciences, Negin Hadisi, +98 44 4432 6311, nhadisi72@yahoo.com
Notes	Completed

NCT04690920	
Trial name or title	Theranostic Implication of complementary medicines against interleukin receptors and Gp-130 proteins
Methods	RCT, active-controlled, open-label study Date of study: December 2020 Location: Pakistan Phase -
Participants	Randomised: 200 participants **Inclusion criteria** • Admitted diagnosed cases of COVID-19 infection on real time polymerase chain reaction (RT-PCR)

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	• Both males and females were included • All participants were on oxygen therapy **Exclusion criteria** • Asthmatics • Pulmonary fibrosis • Chronic obstructive pulmonary disease (COPD) • Allergic to remdesivir • Allergic to Actemra • Refused to take consent
Interventions	**Intervention** • Tocilizumab • Remdesivir **Control interventions** • Standard of care • No intervention
Outcomes	**Primary outcome** **Secondary outcomes** • Oxygen demand (7 to 15 days) • Viral load (7 to 15 days)
Starting date	Study start date: 23 July 2020
Contact information	The University of Lahore, Arif Malik
Notes	Completed

IRCT20200510047383N1	
Trial name or title	Evaluation of the effect of tocilizumab on outcomes of the severe COVID-19 patients
Methods	RCT, active-controlled, double-blind study Date of study: May 2020 Location: Iran Phase 3
Participants	Randomised: 100 participants **Inclusion criteria** • COVID-19 disease confirmed by chest CT and PCR • No pregnancy • No breastfeeding • Negative PPD

(Continued)

	• No bacterial pneumonia (negative sputum and urine culture) • Not use of atorvastatin, alprazolam , amlodipine, MTX, hydroxychloroquine , • Informed consent **Exclusion criteria** • Disapproval of COVID-19 disease by chest computed tomography and PCR positive • PPD Bacterial pneumonia (negative sputum and urine culture) pregnancy • Breastfeeding • Use of atorvastatin, alprazolam, amlodipine, MTX, hydroxychloroquine by the patient • Lack of Informed consent
Interventions	**Intervention:** tocilizumab (8 mg per kilogram of body weight tocilizumab up to a maximum dose of 800 mg) **Control interventions:** standard of care
Outcomes	**Primary outcome** • Mortality **Secondary outcomes**
Starting date	Study start date: 21 May 2020
Contact information	Arak University of Medical Sciences, Mohammadreza Bozorgmanesh, +98 86 3223 1350, mhmm-drz_bzrgmnsh@yahoo.com
Notes	Completed

IRCT20081027001411N4	
Trial name or title	Effect of TOCILIZUMAB (ACTEMRA) on treatment of COVID-19
Methods	RCT, active/placebo-controlled, double-blind study Date of study: June 2020 Location: Iran Phase 2
Participants	Randomised: 40 participants **Inclusion criteria** • COVID-19 patient confirmed by positive PCR test for SARS-CoV-19 or abnormal CT scan finding (bilateral, sub pleural, peripheral ground glass opacities) • Blood oxygen saturation < 90%, respiratory rate > 24 breaths/minute, high CRP rate, lymphopenia < 1100 and not responding to standard COVID-19 treatment **Exclusion criteria** • History of diabetes, high blood pressure, malignancies, positive pro-calcitonin and active infection (Including latent or active TB infection), • Taking immunosuppressive drugs and corticosteroids and abnormal liver enzymes

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Interventions	**Intervention:** tocilizumab (8 mg/kg, if the patient's condition is not stable 2 doses by 12 hours will be administrated, maximum dose: 800 mg) **Control interventions** • Placebo • Standard of care
Outcomes	**Primary outcome** • Mortality **Secondary outcomes**
Starting date	Study start date:-
Contact information	Tehran University of Medical Sciences, Ahmadreza Jamshidi, +98 21 8822 0065, jamshi-da@sina.tums.ac.ir
Notes	Completed

Ongoing studies

NCT04330638	
Trial name or title	Treatment of COVID-19 patients with anti-interleukin drugs
Methods	RCT, active-controlled, open-label study Date of study: April 2020 Location: Belgium Phase 3
Participants	Randomised: 342 participants **Inclusion criteria** • Recent (≥ 6 days of flu-like symptoms or malaise yet ≤ 16 days of flu-like symptoms or malaise prior to randomisation) infection with COVID-19. • Confident COVID-19 diagnosis confirmed by antigen detection test and/or PCR and/or positive serology, or any emerging and validated diagnostic laboratory test for COVID-19 within this period. • In some patients, it may be impossible to get a confident laboratory confirmation of COVID-19 diagnosis after 24 hours of hospital admission because viral load is low and/or problems with diagnostic sensitivity. In those cases, in absence of an alternative diagnosis, and with highly suspect bilateral ground glass opacities on recent (< 24 hours) chest-CT scan (confirmed by a radiologist and pulmonary physician as probable COVID-19), and a typical clinical and chemical diagnosis with signs of cytokine release syndrome, a patient can be enrolled as probable COVID-19 infected. In all cases, this needs confirmation by later seroconversion. • Presence of hypoxia defined as PaO_2/FiO_2 below 350 while breathing room air in upright position or PaO_2/FiO_2 below 280 on supplemental oxygen and immediately requiring high flow oxygen device or mechanical ventilation

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- signs of cytokine release syndrome defined as ANY of the following:
  - serum ferritin concentration > 1000 mcg/L and rising since last 24 hours;
  - single ferritin above 2000 mcg/L in patients requiring immediate high-flow oxygen device or mechanical ventilation;
  - lymphopenia defined as < 800 lymphocytes/microlitre) and 2 of the following extra criteria:
    - ferritin > 700 mcg/L and rising since last 24 hours;
    - increased LDH (above 300 IU/L) and rising last 24 hours;
    - D-dimers > 1000 ng/mL and rising since last 24 hours;
    - CRP above 70 mg/L and rising since last 24 hours and absence of bacterial infection<,
    - if 3 of the above are present at admission, no need to document 24 hour rise
- Chest X-ray or CT scan showing bilateral infiltrates within last 2 days
- Admitted to specialised COVID-19 ward or an ICU ward taking care of COVID-19 patients
- Age ≥ 18 years
- Male or female
- Willing and able to provide informed consent or legal representative willing to provide informed consent

Exclusion criteria

- Patients with known history of serious allergic reactions, including anaphylaxis, to any of the study medications, or any component of the product.
- Mechanical ventilation > 24 hours at randomisation
- Patient on ECMO at time of screening
- Clinical frailty scale above 3. (This frailty score is the patient status before first symptoms of COVID-19 episode.)
- Active bacterial or fungal infection
- Unlikely to survive beyond 48 hours
- Neutrophil count below 1500 cells/microlitre
- Platelets below 50.000/microlitre
- Patients enrolled in another investigational drug study
- ·Patients on high dose systemic steroids (> 20 mg methylprednisolone or equivalent) for COVID-19 unrelated disorder
- Patients on immunosuppressant or immunomodulatory drugs
- Patients on current anti-IL1 or anti-IL6 treatment
- Signs of active tuberculosis
- Serum transaminase levels > 5 times upper limit of normal
- Bowel perforation or diverticulitis
- Pregnant or breastfeeding females (all female participants deemed of childbearing potential by the investigator must have negative pregnancy test at screening)
- Women of childbearing potential must have a negative serum pregnancy test pre-dose on day 1. Women of childbearing potential must consistently and correctly use (during the entire treatment period and 3 months after last treatment) 1 highly effective method for contraception.

Interventions	**Intervention** • Anakinra (SC, 100 mg for 28 days or until hospital discharge) • Siltuximab (IV, 11 mg/kg, single dose) • Tocilizumab (IV, 8 mg/kg with a maximum infusion of 800 mg/injection, single dose) • Anakinra + siltuximab • Anakinra + tocilizumab **Control interventions** Usual care
Outcomes	• **Primary outcome**

(Continued)

	• Time to clinical improvement (day 15) **Secondary outcomes** • Adverse events (28 days) • Serious adverse events (28 days) • Mortality (28 days, 10 to 20 weeks) • Time to 1st use of high-flow oxygen devices, non-invasive or invasive mechanical ventilation in non-ventilated patients (28 days)
Starting date	Study start date: 3 April 2020
Contact information	University Hospital, Ghent, Anja Delporte, +32-9-3320228, anja.delporte@uzgent.be
Notes	Ongoing

NL8504	
Trial name or title	Pre-emptive tocilizumab in hypoxic COVID-19 patients, a prospective randomized trial
Methods	RCT, active-controlled, open-label study Date of study: April 2020 Location: the Netherlands
Participants	Randomised: 354 participants **Inclusion criteria** • Patients 18 years and older • Patients with a diagnosis of COVID-19 based on a compatible clinical presentation AND a positive SARS-CoV-2 PCR on a respiratory sample such as a nasopharyngeal swab, sputum, or BAL fluid • Clinical features compatible with hyperinflammation: - hypoxia, without other explanation for hypoxia than COVID-19 OR - ferritin > 2000 µg/L or doubling of serum ferritin in 20 to 48 hours. Hypoxia is defined according to ASTCT CRS Consensus grading: grade II. (Lee 2019). Inclusion of patients already requiring oxygen administration prior to COVID-19 should be discussed with the study team. • Written informed consent. • Patient is capable of giving informed consent. **Exclusion criteria** • Pregnancy • Allergy to tocilizumab
Interventions	**Intervention:** ·tocilizumab (IV, 8 mg/kg, maximum dose 800 mg, which can be repeated at the same dose after 8 hours if the hypoxia has not improved) **Control interventions:** standard of care (unclear)
Outcomes	**Primary outcome** • Mortality (30 days from randomisation)

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	Secondary outcomes • Percentage of patients who need ICU care • Percentage of patients who develop respiratory failure and need mechanical ventilation.
Starting date	Study start date: 6 April 2020
Contact information	UMCG, Margriet Dijkstra, +31 50 3610468, m.j.dijkstra-tiekstra@umcg.nl
Notes	Ongoing

NCT04348500	
Trial name or title	Clazakizumab (anti-IL- 6 monoclonal) compared to placebo for COVID19 disease
Methods	RCT, placebo-controlled, double-blind study Date of study: April 2020 Location: USA Phase 2

Participants	Randomised: 17 participants
	Inclusion criteria
	• Age > 18 at the time of screening.
	• Participant must be able to understand and provide informed consent.
	• Hospitalised with COVID19+ disease (confirmed by PCR assay from any specimen (e.g. respiratory, blood, urine, stool, other bodily fluid).
	• Not on mechanical ventilation and/or ECMO
	• Evidence of pulmonary involvement with at least 2 of the following:
	  ○ oxygen saturation at rest in ambient air with $SpO_2 \leq 94\%$;
	  ○ tachypnoea with resting respiration rate > 25 breaths/minute;
	  ○ $PaO_2/FiO_2 \leq 300$ mmHg;
	  ○ chest imaging (radiograph, CT scan, or lung ultrasound) with abnormalities consistent COVID-19 pneumonia
	  ○ CRP > 35 mg/L
	Exclusion criteria
	• Previous hypersensitivity or allergic reactions to clazakizumab
	• Lactating or pregnant females.
	• Participants with latent TB and who are not receiving treatment.
	• Participants with active TB
	• A significantly abnormal general serum screening lab result defined as a WBC < 3.0 X 103/ml, a Hgb < 8.0 g/dL, a platelet count < 50 X 103/ml, an SGOT or SGPT > 5X upper limit normal
	• Participation in another clinical trial investigating COVID-19 aimed agents

Interventions	**Intervention:** clazakizumab (IV, 25 mg in 50 cc NS x 1 dose) **Control interventions:** placebo

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Outcomes	**Primary outcome** • Adverse events (14 days) **Secondary outcomes** • Mortality (28 days, 60 days)
Starting date	Study start date: 24 April 2020
Contact information	Cedars-Sinai Medical Center, Stanley Jordan, MD
Notes	Ongoing

NCT04357808	
Trial name or title	Efficacy of subcutaneous sarilumab in hospitalised patients with moderate-severe COVID-19 infection (SARCOVID)
Methods	RCT, active-controlled, open-label study Date of study: April 2020 Location: Spain Phase 2

Participants	Randomised: 30 participants
	Inclusion criteria
	• Age > 18 years
	• Laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other validated commercial or public health assay
	• Documented interstitial pneumonia requiring admission and at least 2 of the following:
	  ◦ fever ≥ 37.8°C (tympanic);
	  ◦ IL-6 in serum ≥ 25 ng / mL (in the absence of a previous dose of prednisone or equivalent > 1 mg / kg) or PCR > 5 mg/dL;
	  ◦ lymphocytes < 600 mm^3;
	  ◦ ferritin > 300 mcg / L that doubles in 24 hours;
	  ◦ ferritin > 600 mcg / L in the 1st determination and LDH > 250 U/L;
	  ◦ D-dimer (> 1 mg / L).
	• Informed verbal or administration consent under urgent conditions, documented in the electronic medical record
	Exclusion criteria
	• Patients who require mechanical ventilation at the time of inclusion
	• AST / ALT values > 5 folds upper normal limit.
	• Neutrophil count below 500 cells / mm^3
	• Platelet count below 50,000 cells / mm^3
	• Documented sepsis or high suspicion by pathogens other than COVID-19
	• Presence of comorbidities that according to clinical judgment could lead to an unfavourable result.

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	• Complicated diverticulitis or intestinal perforation • Current skin infection (e.g. uncontrolled dermopiodermitis) • Immunosuppressive anti-rejection therapy • Pregnancy or lactation • Previous treatment with tocilizumab or sarilumab • Patients participating in some other clinical trial for SARS-CoV-2 infection • Patients with known hypersensitivity or contraindication to sarilumab or excipients
Interventions	**Intervention:** sarilumab (SC, 2 x 200 mg, single dose) **Control interventions:** standard of care
Outcomes	**Primary outcome** • Mean change in clinical status assessment using the 7-point ordinal scale (7 and 14 days from enrolment) • Mortality (30 days from enrolment) **Secondary outcomes** • Time to invasive mechanical ventilation (30 days from enrolment) • Non-serious adverse events (30 days from enrolment)
Starting date	Study start date: 13 April 2020
Contact information	Fundación de Investigación Biomédica - Hospital Universitario de La Princesa, Rosario Garcia de Vicuña, MD PhD
Notes	Ongoing

NCT04359901	
Trial name or title	Sarilumab for patients with moderate COVID-19 disease
Methods	RCT, active-controlled, open-label study Date of study: April 2020 Location: USA Phase 2
Participants	Randomised: 120 participants **Inclusion criteria** • Positive testing for novel coronavirus SARS-CoV-2019 • Patients with moderate COVID-19 disease as defined clinically: ◦ score of 1 to 3 (out of 3) on a modified Brescia COVID respiratory severity score (BCRSS), elements of which include wheezing or inability to speak complete sentences without effort, respiratory rate ≥ 22, O_2 saturation ≤ 90% on room air (or O_2 saturation ≤ 94% on ≥ 2L supplemental oxygen; either is equal to 1 point on the score) all within a 24-hour period prior to enrolment, and/or any worsening of chest X-ray (CXR) findings after COVID-19 diagnosis i. Initial CXR at the time of COVID-diagnosis, or anytime thereafter. Change from baseline CXR prior to COVID-diagnosis would not qualify.

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	○ the BCRSS risk calculation score is available at: mdcalc.com/brescia-covid-respiratory-severity-scale-bcrss-algorithm **Exclusion criteria** • Critical disease, defined by need for mechanical ventilation and/or ICU admission • Expected death within 48 hours • Patients currently taking prednisone > 10 mg/day or on treatment with biologics for chronic inflammatory diseases ○ use of chronic inhaled steroids is NOT an exclusion • Receipt of any IL-6 inhibitor within 3 months prior to enrolment in the trial • Pregnancy, due to lack of foetal monitoring capabilities • Patients enrolled in other interventional clinical trials. Patients enrolled in non-interventional studies or receiving non-FDA-approved drugs for compassionate use are not excluded. • Patients whose goal of care is comfort measures only • Inability to provide informed consent, or absence of a legally authorised representative to provide informed consent. • Severe psychiatric disease that prevents compliance with typical medical care • Participation in another interventional clinical trial for COVID-19
Interventions	**Intervention:** sarilumab (SC,400 mg) **Control interventions:** standard of care
Outcomes	**Primary outcome** · Intubation or death (within 14 days of enrolment) **Secondary outcomes**
Starting date	Study start date: 10 April 2020
Contact information	Westyn Branch-Elliman, VA Boston Healthcare System, Sara Schiller, MPH, 857-364-2012, Sara.Schiller1@va.gov
Notes	Ongoing

NCT04363502	
Trial name or title	Use of the interleukin-6 inhibitor clazakizumab in patients with life-threatening COVID-19 infection
Methods	RCT, placebo-controlled, double-blind study Date of study: April 2020 Location: USA Phase 2
Participants	Randomised: 30 participants **Inclusion criteria** • At least 18 years of age

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- ·Confirmed COVID-19 disease (by Cobas severe acute respiratory syndrome (SARS)-CoV-2 real time RT-PCR using nasopharyngeal swab sample, or equivalent test available to be performed by the Johns Hopkins Medical Laboratories Services). Effort will be made to have the confirmatory test result < 72 hours prior to enrolment however given overall clinical demand this may not be feasible in all cases
- Respiratory failure manifesting as: acute respiratory distress syndrome (defined by a P/F ratio of < 200), OR SpO_2 < 90% on 4L (actual or expected given higher O_2 requirement) OR increasing O_2 requirements over 24 hours, plus 2 or more of the following predictors for severe disease:
  - CRP > 35 mg/L;
  - ferritin > 500 ng/mL;
  - D-dimer > 1 mcg/L;
  - neutrophil-lymphocyte ratio > 4;
  - LDH > 200 U/L;
  - increase in troponin in patient w/out known cardiac disease.
- Has a consent designee willing to provide informed consent on behalf of the patient (this assumes that a mechanically ventilated patients lacks capacity to consent on his/her own behalf. Should it be deemed that the patient has capacity to consent, consent may be obtained from the patient)
- Women of childbearing potential must be willing and able to use at least 1 highly effective contraceptive method for a period of 5 months following the study drug administration. In the context of this study, an effective method is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly such as:
  - combined (oestrogen and progestogen containing) hormonal contraception combined (oestrogen and progestogen containing) hormonal contraception (oral, intravaginal, or transdermal);
  - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable);
  - IUD;
  - IUS;
  - vasectomised partner;
  - bilateral tubal occlusion;
  - true abstinence. when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence, such as calendar, ovulation, symptothermal, postovulation methods, and withdrawal are not acceptable methods of contraception.
- Men must be willing to use a double-barrier contraception from enrolment until at 5 months after the last dose of study drug, if not abstinent

Exclusion criteria

- Evidence of irreversible injury deemed non-survivable even if the pulmonary failure recovers (for example severe anoxic brain injury)
- Known active inflammatory bowel disease
- Known active, untreated diverticulitis
- Known untreated bacteraemia
- Pregnancy. (The protocol will exclude pregnant participants given the lack of overall data on use of clazakizumab in pregnancy however the study team would consider a protocol revision should more than 3 potential pregnant study participants be excluded on this basis).
- Known hypersensitivity to the clazakizumab
- Use of other IL-6 inhibitor investigational drugs at the time of enrolment

Interventions	**Intervention:** clazakizumab (IV, 25 mg, if the CRP does not decrease by 50% within 36 to 48 hours after the 1st dose, a 2nd dose of 25 mg clazakizumab will be given no later than day 3) **Control interventions:** placebo
Outcomes	**Primary outcome** **Secondary outcomes**

(Continued)

Starting date	Study start date: 7 May 2020
Contact information	Johns Hopkins University, Nada Alachkar, MD, 4106149225, nalachk1@jhmi.edu
Notes	Ongoing

NCT04377750	
Trial name or title	The use of tocilizumab in the management of patients who have severe COVID-19 with suspected pulmonary hyperinflammation
Methods	RCT, placebo-controlled, open-label study Date of study: May 2020 Location: Israel Phase 4
Participants	Randomised: 500 participants **Inclusion criteria** • Any gender • Age 18 and older • Informed consent for participation in the study • Virological diagnosis of Sars-CoV2 infection (PCR) • Acute respiratory failure • Radiographic pneumonia, defined as any/ changing new lung infiltrate • Patient breathing spontaneously, required more than 50% oxygen and MEWS score > 7 • If intubated, intubated less than 24 hours with PaO_2/FiO_2 ratio ≤ 200 and PEEP ≥ 5 cm H_2O **Exclusion criteria** • Known hypersensitivity to tocilizumab or its excipients • Patient with a life expectancy of less than 6 months. • Known active infections or other clinical condition that contra-indicate tocilizumab and cannot be treated or solved according to the judgement of the clinician. • Neutrophils < 500 / mmc • Platelets < 40.000 / mmc
Interventions	**Intervention:** tocilizumab(IV, 8 mg/kg up to total dose of 800 mg) **Control interventions:** placebo
Outcomes	**Primary outcome** • Mortality (30 days) **Secondary outcomes**
Starting date	Study start date: 8 April 2020
Contact information	Hadassah Medical Orginisation, Reuven Pizov, Prof., 972-50-6265542, pizovr@hadassah.org.il

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Notes	Ongoing

EUCTR2020-002037-15-ES

Trial name or title	Multicenter, randomized, open-label study to evaluate the efficacy and safety of SOC + sarilumab versus standard of care for the early treatment of COVID-19-pneumonia in hospitalized patients
Methods	RCT, active-controlled, open-label study Date of study: May 2020 Location: Spain Phase 2

Participants	Randomised: 200 participants
	Inclusion criteria
	• Patients willing to provide written informed consent to participate in this study. Witnessed oral consent will be accepted in order to avoid paper handling. Written consent by patient or representatives will be obtained as soon as possible.
	• The patient is at least 18 years of age.
	• The patient is positive for novel coronavirus by real-time RT-PCR
	• The patient is hospitalised for COVID-19 without either mechanical ventilation (invasive or non-invasive) or oxygen mask with reservoir bag and at least 1 of the following:
	  ○ radiographic evidence of pulmonary infiltrates by imaging (chest x-ray, CT scan, etc.); OR
	  ○ clinical assessment (evidence of rales/crackles on exam); AND
	  ○ $SpO_2 \leq 94\%$ on room air that requires supplemental oxygen.
	• More than 7 days between the onset of symptoms (fever, dyspnoea, and/or cough) and treatment administration day. In the absence of fever, cough, or dyspnoea, other symptoms like asthenia, headache, or gastrointestinal symptoms may be considered
	• The patients present progressive elevation of inflammatory parameters suggestive of a hyperinflammatory syndrome:
	  • presence of elevated IL-6 (> 40 pg/mL); OR
	  • elevated D-dimer (> 1.0 mcg/mL), or alternatively, progressive worsening in at least 2 of these inflammatory parameters in the prior 48 hours: CRP, LDH, serum ferritin, lymphopenia, or D-dimer
	Exclusion criteria
	• Requiring mechanical ventilation (invasive or non-invasive) or oxygen mask with reservoir bag at screening
	• Participation in any other clinical trial of an experimental treatment for COVID-19
	• In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
	• Any incompatibility or allergy to the administration of sarilumab or corticosteroids

Interventions	**Intervention**: sarilumab (IV, 200 mg) **Control interventions:** standard of care
Outcomes	**Primary outcome** • Progression to severe respiratory failure (from baseline up to day-15)

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	• ICU admission (from baseline up to day-15) • Mortality (from baseline up to day-15) **Secondary outcomes** • Time to progression to severe respiratory failure
Starting date	Study start date: 25 May 2020
Contact information	Hospital Universitario Puerta de Hierro Majadahonda, 0034911917479, mariabelen.ruiz@salud.madrid.org
Notes	Ongoing

NCT04412291	
Trial name or title	A study in patients with COVID-19 and respiratory distress not requiring mechanical ventilation, to compare standard-of-care with anakinra and tocilizumab treatment the immunomodulation-CoV assessment (ImmCoVA) study
Methods	RCT, active-controlled, open-label study Date of study: June 2020 Location: Sweden Phase 2
Participants	Randomised: 120 participants **Inclusion criteria** • Laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay • SARS-CoV-2 infection with duration at least 7 days (as determined by onset of symptoms) • PaO_2 (or SpO_2)/FiO_2 < 26,8 kPa (200 mmHg) for at least 8 hours, corresponding to 5 litres/minute of Oxygen to maintain SpO_2 at 94% • CRP > 70 mg/L with no non-SARS-CoV-2 infections. • Ferritin > 500 µg/L • At least 2 points on a scale of 0 to 3 where 1 point is awarded for each value of; lymphocytes < 1x 10(9)/L; D-dimer ≥ 0.5 mg/L and; LDH ≥ 8 microkatal/L • Ability to provide informed consent signed by study patient • Willingness and ability to comply with study-related procedures/assessments • Infertile females, willing to comply with effective contraceptive methods for up to 3 months after last dose of study drug. These may include birth control pills, surgical sterilisation of patient or partner or IUD. Non-fertile woman is defined as more than 12 months of amenorrhoea without an alternative medical cause or, in case of ambiguities, an FSH level in the postmenopausal range **Exclusion criteria** • Pregnancy or breast feeding • Ongoing or completed mechanical ventilation • In the opinion of the investigator, unlikely to survive for > 48 hours from screening • In the opinion of the investigator, expected overall survival due to other comorbidities less than 3 months

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	• Chronic impairment of cardiac function NYHA II or higher
	• Severe renal dysfunction eGFR < 30 ml/min
	• Medical history including chronic liver disease with inflammation, fibrosis or cirrhosis including underlying diseases such as alcoholic liver disease, non-alcoholic fatty liver disease, chronic viral hepatitis, alcoholic liver disease, autoimmune liver disease, haemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, cholangitis, or carcinoma
	• Uncontrolled hypertension systolic BP >180 mm Hg, diastolic BP > 110 mm Hg
	• History of hypersensitivity to the study drugs
	• Presence of any of the following abnormal laboratory values at screening:
	  ○ ANC less than 2 x 109/L;
	  ○ AST or ALT greater than 5 x ULN;
	  ○ platelets < 100 x 109/L.
	• Treatment with anakinra, anti-IL 6, anti-IL-6R antagonists, JAKi in the past 30 days or plans to receive during the study period
	• Current treatment with conventional synthetic DMARD)/immunosuppressive agents
	• Use of chronic oral corticosteroids for a non-COVID-19-related condition in a dose higher than prednisone 10 mg or equivalent per day
	• History of, or current autoimmune or inflammatory systemic or localised disease(s) other than rheumatoid arthritis
	• Acute systemic infection; verified by blood cultures systemic bacterial infection, systemic fungi-infection or prosthesis-related infection
	• History of stem-cell or solid organ transplantation
	• Known active TB, history of incompletely treated TB, suspected or known extrapulmonary TB, suspected or known systemic bacterial or fungal infections
	• Diagnosis of, or suspicion of HIV infection, acute hepatitis A and/or chronic hepatitis B and/or C
	• Previous history of gastrointestinal ulceration or diverticulitis.
	• Patients who have received immunosuppressive antibody therapy within the past 3 months, including intravenous immunoglobulin or plans to receive during the study period
	• Participation in any clinical research study evaluating an IPh or therapy within 3 months and less than 5 half-lives of IP prior to the screening visit. The use of remdesivir in the context of a single-arm remdesivir compassionate use protocol is permitted)
	• Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study

Interventions	**Intervention** • Anakinra (IV, anakinra 400 mg per day, divided in 4 doses of 100 mg, for 7 days) • Tocilizumab (IV, 8 mg/kg for up to max 800 mg, single infusion, another dose of 8 mg/kg may be administered after earliest 2 days) **Control interventions** • Standard of care
Outcomes	**Primary outcome** **Secondary outcomes** • Mortality (up to day 29) • Patients requiring initiation of mechanical ventilation (up to day 29) • Mean change in the 8-point ordinal scale (up to day 29) • Time to clinical improvement (up to day 29)
Starting date	Study start date: 11 June 2020

(Continued)

Contact information	Karolinska University Hospital, Jonas Sundén-Cullberg, +46-8-58580000, Jonas.sunden-cullberg@sll.se
Notes	Ongoing

NCT04412772	
Trial name or title	A RCT - safety & efficacy of tocilizumab - Tx of severe COVID-19: ARCHITECTS
Methods	RCT, placebo-controlled, double-blind study Date of study: June 2020 Location: USA Phase 3

Participants	Randomised: 300 participants
	Inclusion criteria
	• Hospitalised with COVID-19 pneumonia, based on chest X-ray or CT scan; AND
	• Evidence of hyperinflammation: IL-6 > 40pg/mL (if available);OR
	• CRP > 2 mg/dL; OR
	• Ferritin > 2000 ng/mL AND iv. 1 or more of the following:
	  ○ impending need for requiring invasive or non-invasive mechanical ventilation; OR
	  ○ shock requiring vasopressor (without evidence of bacterial / fungal infection); OR
	  ○ need for ECMO; OR
	  ○ severe, refractor ARDS (PaO_2/FiO_2< 200 mmHg).
	Exclusion criteria
	• Active tuberculosis infection based on history
	• Suspected active bacterial, fungal, viral, or other infection (besides COVID-19)
	• In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
	• Have received oral anti-rejection or immunomodulatory drugs (including tocilizumab) with the past 6 months
	• Participating in other drug clinical trials (participation in COVID-19 trials allowed)
	• Self-reported pregnant or breastfeeding
	• Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
	• ALT or AST > 10 x ULN detected within 24 hours at baseline
	• ANC < 1000/mL at baseline
	• Platelet count < 50,000/mL at baseline

Interventions	**Intervention:** tocilizumab (IV, 8 mg/kg for up to max 800 mg, single infusion, 1 additional dose may be given if clinical symptoms worsen) **Control interventions:** placebo
Outcomes	**Primary outcome** • Clinical status on a 7-point ordinal scale (up to day 28)

(Continued)

	Secondary outcomes • Clinical improvement (up to day 28) • Mechanical ventilation (up to day 28)
Starting date	Study start date: 12 June 2020
Contact information	Queen's Medical Centre, Todd Seto, tseto@queens.org
Notes	Ongoing

EUCTR2020-001390-76-IT	
Trial name or title	A phase 3, randomized, open-labeled, multi-center study comparing clinical efficacy and safety of intravenous sarilumab plus standard of care compared to standard of care, in the treatment of patients with severe COVID-19 pneumonia.
Methods	RCT, active-controlled, open-label study Date of study: June 2020 Location: Italy Phase 3

Participants	Randomised: 171 participants
	Inclusion criteria
	• Age = 18 years
	• Signed informed consent provided by the patient, or by the patient's legally authorised representative(s), as applicable. Orally provisions could be considered in emergency conditions if deemed necessary by the investigator (signature of the informed consent will occur if and as soon as clinical conditions improve).
	• Virological diagnosis of SARS-CoV-2 infection (SARS-CoV-2 infection confirmed by PCR test or positive serology)
	• Evidence of pulmonary infiltrates at CT scan or Chest Xray
	• Oxygen saturation (SpO_2) at rest without oxygen supplementation < 93% or PaO_2/FiO_2 < 300 at rest in patients requiring oxygen supplementation (either Venturi mask or cPAP or NIV).
	• Evidence of hyperinflammation defined as at least 2 of the following:
	  ◦ blood lymphocytes < 1000/mm3;
	  ◦ ferritin > 500 ng/mL;
	  ◦ LDH > 300 U/L;
	  ◦ D-dimers > 1000 ng/mL;
	  ◦ C-reactive protein > 3 mg/dL.
	• Indication to start antiviral therapy with either hydroxychloroquine or lopinavir/ritonavir as regular clinical practice (or patients who have already started/finished antiviral therapy for SARS-CoV-2)
	• Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method (s) of contraception
	Exclusion criteria
	• Known hypersensitivity to sarilumab or its excipients

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	• Known active infections or other clinical condition that contraindicate sarilumab and cannot be treated or solved according to the judgement of the clinician • Patient being treated with immunomodulators or anti-rejection drugs • Pregnancy/lactation • Neutrophils count < 500 cell/mm^3 • Platelets count < 50.000/mm^3 • ALT / AST> 5 times the upper limit of the normality • Bowel diverticulitis or perforation • Existence of any life-threatening co-morbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion • Severe hepatic dysfunction • Creatinine clearance < 30 ml/min/1.73 m^2 • Mechanical ventilation or ECMO • Enrolment in another concurrent clinical interventional study • Intake of an investigational drug within 3 months
Interventions	**Intervention:** ·sarilumab (IV, 400 mg) **Control interventions:** standard of care
Outcomes	**Primary outcome** • Time to clinical improvement (every visit) **Secondary outcomes** • Mortality (30 days from baseline) • Time to death • Time to mechanical ventilation or extracorporeal membrane oxygenation • Serious adverse events
Starting date	Study start date: 27 April 2020
Contact information	Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani, 0655170546, immunodeficienzevirali@inmi.it
Notes	Ongoing

CTRI/2020/05/025369	
Trial name or title	A study on treatment of COVID-19 patients with study drug along with standard of care
Methods	RCT, active-controlled, open-label study Date of study: May 2020 Location: India Phase 3
Participants	Randomised: 180 participants **Inclusion criteria**

(Continued)

	• Male or female participants who are ≥ 18 years of age, on the day of signing informed consent. • Patient or legally acceptable representative (LAR) willing to give informed consent before study procedure. • Hospitalised with COVID-19 infection confirmed per WHO criteria (including a positive PCR of any specimen; e.g. respiratory, blood, urine, stool, other bodily fluid). • Moderate to severe COVID 19 infection (moderate disease – increased respiratory rate 15 to 30/minute and SpO_2 90% to 94%; and severe disease - respiratory rate ≥ 30/minute and/or SpO_2 < 90% on room air, or ARDS or septic shock **Exclusion criteria** • Known severe allergic reactions to TCZ or other monoclonal antibodies • Active tuberculosis (TB) infection • Suspected or active bacterial, fungal, viral (except treated HCV or HBV infection), or other infection (besides COVID-19). • In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments • Have received oral anti-rejection or immunomodulatory drugs (including TCZ) with in the past 6 months • Participating in other drug clinical trials • Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination • Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomisation • Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient safe participation in and completion of the study • Definite diagnosis of rheumatic immune related diseases. • Administration of steroids equivalent to methylprednisolone at a dose > 1 mg/kg/day) at screening/baseline • Absolute neutrophil count < 500, platelet count < 50,000 per microlitre at screening/baseline • AL) or (AST > 10 times upper limit of normal detected with-in 24 hours at screening/baseline
Interventions	**Intervention:** tocilizumab (IV, 6 mg/kg for up to max 480 mg, single infusion) **Control interventions:** standard of care
Outcomes	**Primary outcome** • Progressive COVID 19 disease from moderate to severe, or from severe disease to death (up to day 14) **Secondary outcomes** • Time to clinical improvement (up to day 28) • Clinical improvement (up to day 28) • Incidence of mechanical ventilation (up to day 28) • Incidence of intensive care (up to day 28) • Mortality (days 7, 14, 21 and 28)
Starting date	Study start date: 30 May 2020
Contact information	Medanta Institute of Education and Research (MIER), 01244855100, pooja.sharma@medanta.org
Notes	Ongoing

NCT04494724	
Trial name or title	Clazakizumab vs. placebo - COVID-19 infection
Methods	RCT, placebo-controlled, double-blind study Date of study: July 2020 Location: USA Phase 2

Participants	Randomised: 60 participants
	Inclusion criteria
	• Age > 18 at the time of screening.
	• Participant or LAR must be able to understand and provide informed consent.
	• Hospitalised with coronavirus disease (COVID-19) confirmed by PCR assay from any specimen (e.g. respiratory, blood, urine, stool, other bodily fluid) within the prior 72 hours.
	• · CRP > 3.5 mg/dL
	• · Evidence of pulmonary involvement with at least 2 of the following:
	  ○ oxygen saturation at rest in ambient air with peripheral capillary oxygen saturation (SpO_2) ≤ 94%
	  ○ tachypnoea with resting respiration rate > 25 breaths/minute
	  ○ Partial pressure of oxygen (PaO_2)/initial fraction of inspired oxygen (FiO_2) ≤ 300 mmHg
	  ○ Chest imaging (radiograph, CT, or ultrasound) with abnormalities consistent COVID-19 pneumonia
	Exclusion criteria
	• Previous hypersensitivity or allergic reactions to clazakizumab
	• Lactating or pregnant females
	• Patients with latent TB and who are not receiving treatment
	• Patients with active TB
	• Patients with known active inflammatory bowel disease, untreated diverticulitis, or gastrointestinal perforation
	• Requiring mechanical ventilation or ECMO
	• A significantly abnormal general serum screening lab result defined as a WBC count < 3.0 X 10^3/mL, a haemoglobin (Hgb) < 8.0 g/dL, a platelet count < 50 X 10^3/mL, an AST or ALT > 5 times ULN
	• Participation in another clinical trial investigating COVID-19-aimed agents
	• Presence of any medical or psychosocial condition, which the investigator believes, would hinder adherence to the study requirements.

Interventions	**Intervention:** clazakizumab (IV, 25 mg in 50 mL of 0.9% saline) **Control interventions:** placebo
Outcomes	**Primary outcome** • Adverse events (during the first 24 hours) **Secondary outcomes** • Mechanical ventilation and/or extracorporeal membrane oxygenation (14 days) • Mortality (28 days, 60 days) • Clinical improvement (28 days)

(Continued)

Starting date	Study start date: 13 July 2020
Contact information	Houston Methodist Hospital, Isioma Agboli, 713-441-6311, iagboli@houstonmethodist.org
Notes	Ongoing

NCT04577534	
Trial name or title	Use of tocilizumab in the inflammatory phase of COVID-19 / new coronavirus disease
Methods	RCT, active-controlled, open-label study Date of study: October 2020 Location: Finland Phase 3

Participants	Randomised: 90 participants
	Inclusion criteria
	• Written informed consent obtained
	• Hospitalised with COVID-19 disease
	• Age ≥ 18 years
	• SARS CoV-2 NhO posit
	• Sp = 2 < /93% on ambient air or respiratory rate > 30 /min
	• Any 2 of the 4:
	  ○ P-IL-6 > 2 x ULN / P-ferritin > 2 x ULN / P-FIDD > 1.5 mg/L / P- CRP > 40 mg/L without obvious presence of bacterial infection (normal values: P -IL-6 < 5.9 ng/L;
	  ○ P-ferritin, men 30 to 400 mickrog/l, women 13 to 150 mikrog/l;
	  ○ P-FIDD (Fibrin degradation products, D-dimer) <0.5 mg/L;
	  ○ P-CRP < 10 mg/L).
	Exclusion criteria
	• Known severe allergic reactions to monoclonal antibodies
	• Active confirmed tuberculosis with ongoing treatment or obvious tuberculosis or obvious other bacterial, fungal or viral infection (besides COVID-19)
	• In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
	• Long-term oral anti-rejection or immunomodulatory drugs (including corticosteroids equivalent to methylprednisolone 15 mg/day)
	• Pregnant or lactating women. If needed, exclusion of pregnancy should be performed by laboratory test (U-hCG-O).
	• Participating in other drug clinical trials
	• Absolute neutrophil count < 1 x 10E9/L
	• Platelet count < 50 x 10E9/L
	• ALT > 10 x ULN

Interventions	**Intervention:** tocilizumab (IV, single infusion according to weight of patient) **Control interventions:** standard of care

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Outcomes	**Primary outcome** • Clinical status (28 days) **Secondary outcomes** • Time to clinical improvement (28 days) • Time to decline of at least 2 categories (28 days) • Mechanical and/or non-invasive ventilation (28 days) • ICU stay (28 days) • Mortality (28 days)
Starting date	Study start date: 14 August 2020
Contact information	Turku University Hospital, Jarmo Oksi, +358 40 5414813, jarmo.oksi@utu.fi
Notes	Ongoing

EUCTR2020-001290-74-ES	
Trial name or title	Efficacy and safety of sarilumab in the early treatment of hospitalized patients with mild-moderate pneumonia and COVID19 infection versus standard of care
Methods	RCT, active-controlled, open-label study Date of study: April 2020 Location: Spain Phase 3
Participants	Randomised: 216 participants **Inclusion criteria** • More than18 years • Diagnostic confirmation of COVID19 infection (PCR) and radiological diagnosis of pneumonia • MEWS less than 3 and CURB 65 less than or equal to 1, IL6 greater than or equal to 20 pg / mL **Exclusion criteria** • AST / ALT> 5 X LSN- neutrophils < 500 cell / mm^3 • Lymphocytes < 400 cell • Platelets < 50,000 cell / mm^3 • Creatinine clearance (CCL) < 30 mL / min • Documented sepsis and active infection by other pathogens other than COVID-19- • Presence of comorbidities that may lead to a poor prognosis according to clinical criteria • Complicated diverticulitis or intestinal perforation • Ongoing skin infection (e.g. uncontrolled pyodermitis with antibiotic treatment) • Anti-rejection immunosuppressive therapy • Other biological treatments • At the investigator's discretion, survival less than 48 hours from screening • Treatment with anti-IL 6, anti-IL-6R antagonists or with Janus kinase inhibitors (JAKi) in the last 30 days or plans to receive during the study period

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	• Current treatment with conventional synthetic disease modifying antirheumatic drugs (DMARDs) / immunosuppressive agents • History of current systemic or localised autoimmune or inflammatory diseases, other than rheumatoid arthritis • Known active TB, history of incompletely treated TB, suspected or known extrapulmonary TB, suspected or known systemic bacterial or fungal infections • Patients who have received immunosuppressive antibody therapy in the last 5 months, including intravenous immunoglobulin, or who plan to receive it during the study period. • Participation in any clinical research study evaluating a research product or therapy (PI) within 3 months and less than 5 PI half lives before the screening visit. (The use of remdisivir in the context of a compassionate use remdisivir one-arm is allowed.) • Pregnancy • Hypersensitivity to sarilumab and / or to some of its excipients. • Any finding of the physical examination and/or history of any disease that, in the opinion of the study investigator, may confuse the study results or represent an additional risk for the patient due to their participation in the study.
Interventions	**Intervention:** sarilumab **Control interventions:** usual care
Outcomes	**Primary outcome** • Time to clinical improvement (28 days) **Secondary outcomes** • Mortality (28 days) • Mechanical ventilation • Time to death • Serious adverse events
Starting date	Study start date: 11 April 2020
Contact information	Consorci PSMAR, Ana Aldea, +34933160490, aaldea@imim.es
Notes	Ongoing

EUCTR2020-001767-86-IE	
Trial name or title	An open-label, multi-centre, randomised trial comparing different doses of single-dose tocilizumab in adults with severe, non-critical, PCR-confirmed COVID-19 infection with evidence of progressive
Methods	RCT, active-controlled, open-label study Date of study: April 2020 Location: Ireland Phase 2
Participants	Randomised: 90 participants **Inclusion criteria**

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	• Confirmed SARS-CoV2 infection (as defined by positive PCR)
	• Evidence of hyper inflammatory state as evidenced by at least 3 of the following:
	  ○ documented temperature > 38°C in the past 48 hours;
	  ○ IL6 > 40 pg/mL, or in its absence D-dimer > 1.5 µgFEU/mL;
	  ○ elevated CRP (> 100 mg/L) and/or a 3-fold increase since presentation;
	  ○ elevated ferritin X 5 ULN;
	  ○ elevated LDH (above the ULN);
	  ○ elevated fibrinogen (above the ULN).
	• Pulmonary infiltrates on chest imaging
	• Moderate to severe respiratory failure as defined by $PaO_2/FiO_2 \leq 300$ mmHg
	• Aged 18 years or older
	
	Exclusion criteria
	
	• Primary or secondary immunodeficiency
	• Use of significant immunosuppressive therapy in the last 3 months (not including hydroxychloroquine or short course of corticosteroids (defined as < 400mg cumulative dose)
	• Active malignancy requiring treatment
	• Known active current or history of recurrent bacterial,mycobacterial, fungal or viral infections including history of untreated latent TB
	• History of diverticulitis or chronic ulcerative GI disease that might predispose to GI perforation
	• Severe allergic reaction to monoclonal antibodies
	• Pregnancy or breast feeding
	• AST/ALT with values greater than 10 times normal levels or history of significant liver disease that in the opinion of the investigator precludes use of an investigational agent
	• Neutrophils < 0.5 x 109/L
	• Platelets < 50 x 109/L
	• Documented, uncontrolled sepsis caused by pathogen(s) other than COVID-19
	• Presence of co-morbidities (including cognitive impairment and/or frailty) that, in the opinion of the investigator, should preclude use of an investigational agent
	• Current skin or soft tissue infection not controlled by antibiotics
	• Body weight ≤ 30kg

Interventions	**Intervention:** tocilizumab (IV, single dose, different doses) **Control interventions:** standard of care
Outcomes	**Primary outcome** • Progression to intubation and ventilation, non-invasive ventilation or death (day 8) **Secondary outcomes** • Serious adverse events (day 8) • Mortality (day 14 and 28) • Time to viral negative conversion
Starting date	Study start date: 25 June 2020
Contact information	University College Dublin, crc.monitoring@ucd.ie
Notes	Ongoing

NCT04659772	
Trial name or title	A study to evaluate clazakizumab in patients with life-threatening COVID-19 infection.
Methods	RCT, placebo-controlled, blind-label study Date of study: December 2020 Location: USA Phase 2
Participants	Randomised: 30 participants **Inclusion criteria** • ≥ 18 years of age. • Confirmed COVID-19 disease (by Cobas SARS-CoV-2 real time RT-PCR using nasopharyngeal swab sample, or equivalent test available to be performed by Mayo Clinic clinical laboratory). Effort will be made to have the confirmatory test result < 72 hours prior to enrolment however given overall clinical demand this may not be feasible in all cases. • Respiratory failure manifesting as: acute respiratory distress syndrome (defined by a P/F ratio of < 200), OR SpO_2 < 90% on 4L (actual or expected given higher O_2 requirement) OR increasing O_2 requirements over 24 hours, PLUS 2 or more of the following predictors for severe disease: o CRP > 35 mg/L; o ferritin > 500 ng/mL; o D-dimer > 1 mcg/L; o neutrophil-lymphocyte ratio > 4; o LDH > 200 U/L; o increase in troponin in patient w/out known cardiac disease. • Has a consent designee willing to provide informed consent on behalf of the patient (this assumes that a mechanically-ventilated patients lacks capacity to consent on his/her own behalf. Should it be deemed that the patient has capacity to consent, consent may be obtained from the patient) • Women of childbearing potential must be willing and able to use at least 1 highly effective contraceptive method for a period of 5 months following the study drug administration. In the context of this study, an effective method is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly such as: o combined (oestrogen and progestogen containing) hormonal contraception combined (oestrogen and progestogen containing) hormonal contraception (oral, intravaginal, or transdermal); o progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); o IUD; o IUS; o vasectomised partner; o bilateral tubal occlusion; o true abstinence. when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence, such as calendar, ovulation, symptothermal, postovulation methods, and withdrawal are not acceptable methods of contraception. • Men must be willing to use a double-barrier contraception from enrolment until at 5 months after the last dose of study drug, if not abstinent • A participant, or an appropriate representative to the participant, will have the opportunity to consent with regard to the inclusion criteria above **Exclusion criteria** • < 18 years of age

(Continued)

	• Evidence of irreversible injury deemed non-survivable even if the pulmonary failure recovers (for example severe anoxic brain injury) • Known active inflammatory bowel disease • Known active, untreated diverticulitis • Known untreated bacteraemia • Pregnancy (the protocol will exclude pregnant participants given the lack of overall data on use of clazakizumab in pregnancy however the study team would consider a protocol revision should more than 3 potential pregnant study participants be excluded on this basis) • Known hypersensitivity to the clazakizumab • Vulnerable participants will not be excluded. This study is designed to include any patients deemed at risk for imminent death, and the opportunity to enrol will not be withheld provided the participant meets the above inclusion and exclusion criteria
Interventions	**Intervention:** clazakizumab(IV, single dose, 25 mg, repeated dose for patients who fail expected decrease in inflammatory markers) **Control interventions:** placebo
Outcomes	**Primary outcome** • Adverse events (60 days) **Secondary outcomes**
Starting date	Study start date: -
Contact information	Mayo Clinic in Arizona, Ayan Sen
Notes	Ongoing

NCT04343989	
Trial name or title	A randomized placebo-controlled safety and dose-finding study for the use of the IL-6 inhibitor clazakizumab in patients with life-threatening COVID-19 Infection
Methods	RCT, placebo-controlled, double-blind study Date of study: April 2020 Location: USA Phase 2
Participants	Randomised: 90 participants **Inclusion criteria** • At least 18 years of age • Confirmed COVID-19 disease (by Cobas SARS-CoV-2 real time RT-PCR using nasopharyngeal swab sample, or equivalent test available to be performed by the NYU Langone clinical laboratory). Effort will be made to have the confirmatory test result < 72 hours prior to enrolment however given overall clinical demand this may not be feasible in all cases.

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- Respiratory failure manifesting as: acute respiratory distress syndrome (defined by a P/F ratio of < 200), OR SpO_2 < 90% on 4L (actual or expected given higher O_2 requirement) OR increasing O_2 requirements over 24 hours, PLUS 2 or more of the following predictors for severe disease:
  - CRP > 35 mg/L;
  - ferritin > 500 ng/mL
  - D-dimer > 1 mcg/L<,
  - neutrophil-lymphocyte ratio > 4;
  - LDH > 200 U/L;
  - increase in troponin in patient w/out known cardiac disease.
- Has a consent designee willing to provide informed consent on behalf of the patient (this assumes that a mechanically-ventilated patient lacks capacity to consent on his/her own behalf. Should it be deemed that the patient has capacity to consent, consent may be obtained from the patient.)
- Women of childbearing potential must be willing and able to use at least 1 highly effective contraceptive method for a period of 5 months following the study drug administration. In the context of this study, an effective method is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly such as:
  - combined (oestrogen and progestogen containing) hormonal contraception combined (oestrogen and progestogen containing) hormonal contraception (oral, intravaginal, or transdermal);
  - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable);
  - IUD
  - IUS;
  - vasectomised partner;
  - bilateral tubal occlusion;
  - true abstinence. when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence, such as calendar, ovulation, symptothermal, postovulation methods, and withdrawal are not acceptable methods of contraception.
- Men must be willing to use a double-barrier contraception from enrolment until at 5 months after the last dose of study drug, if not abstaining

Exclusion criteria

- Evidence of irreversible injury deemed non-survivable even if the pulmonary failure recovers (for example severe anoxic brain injury)
- Known active inflammatory bowel disease
- Known active, untreated diverticulitis
- Known untreated bacteraemia
- Pregnancy. (The protocol will exclude pregnant participants given the lack of overall data on use of clazakizumab in pregnancy however the study team would consider a protocol revision should more than 3 potential pregnant study participants be excluded on this basis).
- Known hypersensitivity to the clazakizumab

Interventions	**Intervention:** clazakizumab (IV, 25 mg/12.5 mg, the CRP does not decrease by 50% within 36 to 48 hours after the 1st dose, a 2nd dose of 25 mg/12.5 mg will be given no later than day 3) **Control interventions:** placebo
Outcomes	**Primary outcome** • Serious adverse events (60 days) **Secondary outcomes** • Cumulative incidence of intubation (14 days) • Mortality (60 days)

(Continued)

Starting date	Study start date: 31 March 2020
Contact information	NYU Langone Health, Bonnie Lonze, MD, 212-263-8365, bonnie.lonze@nyulangone.org
Notes	Ongoing

NCT04357860	
Trial name or title	Clinical trial of sarilumab in adults with COVID-19
Methods	RCT, active-controlled, open-label study Date of study: April 2020 Location: Spain Phase 2
Participants	Randomised: 120 participants **Inclusion criteria** • Age ≥ 18 years and < 75 years • Admission for confirmed respiratory symptoms to COVID-19 based on a positive PCR in a sample of the respiratory tract in the local laboratory in the absence of respiratory distress syndrome requiring ONAF or mechanical ventilation • Interstitial pneumonia confirmed by chest radiography or CT • IL-6 levels > 40 pg/mL. In its absence, D-Dimer (DD) > 1500 or > 1000 may be included if progressive increases are documented • Negative pregnancy test in women of childbearing age • Signature of informed consent **Exclusion criteria** • SOFA score > 6 points • Patient who, in the researcher's opinion, is not a subsidiary of invasive mechanical ventilation • Neutrophil count < 2 x 103 / µL • Platelet count < 100 x 103 / µL • ALT or AST levels > 5 times the upper limit of normal • Severe renal failure (CrCr < 30 mL / min) • Active bacterial infectious process • Active TB, history of not completing treatment against tuberculosis, suspicion of extrapulmonary tuberculosis • History of intestinal ulcer or diverticulitis • History of hypersensitivity reactions to sarilumab or its excipients • Treatment with TNF antagonists • Previous treatment with anti-IL6 in the previous 30 days • Chronic prior treatment with corticosteroids at doses greater than 0.5 mg / kg / day of prednisone or equivalent. Yes, inhaled and topical corticosteroids are acceptable • Concomitant treatment with immunomodulators, among which are Vitamin D or statins. Macrolides such as azithromycin are acceptable • Patients on immunosuppressive treatment for any cause • HIV-infected patients with CD4 < 200 / mm^3

(Continued)

	• Past or current history of autoimmune disease or systemic inflammatory disease • Patients who have received or are planning therapy with immunomodulatory antibodies, including immunoglobulins • Participation in any clinical trial that evaluated any investigational product in the last 3 months or less than 5 half-lives of the investigational product • Pregnancy • Any other condition that, in clinical judgment, prevents adherence to the patient's protocol
Interventions	**Intervention:** sarilumab (SC, 200 mg/400 mg, up to 14 days) **Control interventions:** standard of care
Outcomes	**Primary outcome** • Ventilation requirements (at day 28 or when the participant is discharged) **Secondary outcomes** • Mortality (at day 28 or when the participant is discharged) • Negative viral conversion (at day 28 or when the participant is discharged) • Time to clinical improvement (at day 28 or when the participant is discharged) • Proportion of patients requiring invasive mechanical ventilation (at day 28 or when the participant is discharged) • Adverse events
Starting date	Study start date: -
Contact information	Hospital Universitario Reina Sofía, Antonio Luque, 0034671596070, uicec@imibic.org
Notes	Ongoing

Studies that are registered but not recruiting

NCT04381052	
Trial name or title	Study for the use of the IL-6 Inhibitor clazakizumab in patients with life-threatening COVID-19 infection
Methods	RCT, placebo-controlled, double-blind study Date of study: May 2020 Location: USA Phase 2
Participants	Randomised: 30 participants **Inclusion criteria** • At least 18 years of age • Confirmed COVID-19 disease (by Cobas SARS-CoV-2 real time reverse transcription polymerase chain reaction (RT-PCR) using nasopharyngeal swab sample, or equivalent test available to be performed by the Columbia University Irving Medical Center (CUIMC)/New York Presbyterian (NYP) clinical laboratory). Effort will be made to have the confirmatory test result < 72 hours prior to enrolment however given overall clinical demand this may not be feasible in all cases.

(Continued)

- Respiratory failure manifesting as: ARDS (defined by a P/F ratio of < 200), OR oxygen saturation (SpO_2) < 90% on 4 litres (L) (actual or expected given higher O_2 requirement) OR increasing O_2 requirements over 24 hours, plus 2 or more of the following predictors for severe disease:
  - CRP > 35 mg/L<,
  - ferritin > 500 ng/mL<,
  - D-dimer > 1 mcg/L<,
  - neutrophil-lymphocyte ratio > 4<,
  - LDH > 200 U/L;
  - increase in troponin in patient w/out known cardiac disease.
- Has a consent designee willing to provide informed consent on behalf of the patient (this assumes that a mechanically-ventilated patient lacks capacity to consent on his/her own behalf. Should it be deemed that the patient has capacity to consent, consent may be obtained from the patient)
- Women of childbearing potential must be willing and able to use at least 1 highly effective contraceptive method for a period of 5 months following the study drug administration. In the context of this study, an effective method is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly such as:
  - combined (oestrogen and progestogen containing) hormonal contraception combined (oestrogen and progestogen containing) hormonal contraception (oral, intravaginal, or transdermal);
  - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable);
  - IUD;
  - IUS;
  - vasectomised partner;
  - bilateral tubal occlusion;
  - true abstinence when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence, such as calendar, ovulation, symptothermal, postovulation methods, and withdrawal are not acceptable methods of contraception.
- Men must be willing to use a double-barrier contraception from enrolment until at 5 months after the last dose of study drug, if not abstinent

Exclusion criteria

- Evidence of irreversible injury deemed non-survivable even if the pulmonary failure recovers (for example severe anoxic brain injury)
- Known active inflammatory bowel disease
- Known active, untreated diverticulitis
- Known untreated bacteraemia
- Pregnancy. (The protocol will exclude pregnant participants given the lack of overall data on use of clazakizumab in pregnancy however the study team would consider a protocol revision should more than 3 potential pregnant study participants be excluded on this basis)
- Known hypersensitivity to the clazakizumab

Interventions	**Intervention:** clazakizumab (IV, 25 mg, if the CRP does not decrease by 50% within 36 to 48 hours after the 1st dose, a 2nd dose of placebo will be given no later than day 3) **Control interventions:** placebo
Outcomes	**Primary outcome** • Serious adverse events (60 days) **Secondary outcomes** • Cumulative Incidence of Intubation (14 days) • Mortality (60 days)

(Continued)

Starting date	Study start date: -
Contact information	Columbia University, David J. Cohen, MD, 212-305-3273, djc5@cumc.columbia.edu
Notes	Registered but not recruiting

NCT04452474	
Trial name or title	Study of the efficacy and safety of a single administration of olokizumab vs. placebo in addition to standard treatment in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)
Methods	RCT, placebo-controlled, double-blind study Date of study: June 2020 Location: USA Phase 2/3

Participants	Randomised: 376 participants
	Inclusion criteria
	• COVID-19 diagnosis (confirmation of the presence of SARS-CoV-2 virus by rt-PCR) OR sample collection for SARS-CoV-2 virus rt-PCR if the results of SARS-CoV-2 virus rt-PCR are not available yet
	• Dated informed consent for participation in this study signed by the patient, or by the legally acceptable representative or when prior consent of the patient is not possible, and the participant's legally acceptable representative is not available, documented approval/favourable opinion by the IRB/IEC
	• SpO_2 ≤ 93% (room air) or respiratory rate greater than 30/min (room air) or oxygenation index PaO_2/FiO_2 ≤ 300 mmHg (or SpO_2/FiO_2 ≤ 315 in the case PaO_2/FiO_2 assessment is not available (supplementary oxygen)
	• Computed tomography findings: features consistent with bilateral COVID-19 viral pneumonia and no alternative explanation for these findings
	Exclusion criteria
	• Presence of any of the following laboratory abnormalities:
	  ◦ absolute neutrophil counts < 0,5 x 10^9/L
	  ◦ WBCl count < 2 x 10^9/L
	  ◦ platelet count < 50 x 10^9/L
	  ◦ ALT and/or AST ≥ 3,0 x ULN
	• Kidney injury with creatinine clearance < 30 mL/min
	• Hypersensitivity to OKZ, and/or its components
	• Septic shock (need for vasopressors to maintain mean arterial pressure ≥ 65 mm Hg and lactate ≥ 2 mmol / L in the absence of hypovolaemia).
	• Estimated survival of less than 24 hours regardless of treatment
	• History of perforation of the gastrointestinal tract, history of diverticulitis

(Continued)

	• Recent (less than 5 half-lives), current or planned during the current study period use of immunosuppressive drugs:
	  ◦ biologics (except OKZ) with immunosuppressive effect, including, but not limited to:
	  ■ Interleukin-1 (IL-1) inhibitors (anakinra, rilonacept, canakinumab);
	  ■ IL-6 inhibitors (tocilizumab, sarilumab, siltuximab, etc.);
	  ■ IL-17A inhibitors (secukinumab, etc.);
	  ■ tumour necrosis factor-alpha (TNF-alpha) inhibitors (infliximab, adalimumab, etanercept, etc);
	  ■ anti-B-cells therapy, etc.
	  ◦ other immunosuppressive drugs (excluding methotrexate in dose up to 25 mg/week), including but not limited to:
	  ■ glucocorticoids in high doses (> 1 mg / kg equivalent of methylprednisolone) orally and parenterally;
	  ■ JAK inhibitors; etc.
	• Concurrent participation in another clinical trial during 30 days before screening
	• Pregnancy or lactation
	• A history of active TB, or active TB suspected by the Investigator
	• Administration of plasma from COVID-19 reconvalescent donors for 4 weeks prior to the patient's inclusion in the study and/or planned administration during the study
	• Patients who deteriorated into Category 4 of the 5-point clinical status scale within more than the last 24 hours

Interventions	**Intervention:** · olokizumab (SC, 64 mg, single dose on day 1) **Control interventions:** placebo
Outcomes	**Primary outcome** • Clinical improvement (day 29) **Secondary outcomes** • Clinical status distribution (from day 2 to 15, 29, 60) • Mortality (from day 1, to 29)
Starting date	Study start date:-
Contact information	R-Pharm, Mikhail Samsonov
Notes	Registered but not recruiting

ACTRN12620000580976	
Trial name or title	Tocilizumab for the treatment of COVID-19 in intensive care patients: effect on days free of ventilatory support
Methods	RCT, active-controlled, open-label study Date of study: April 2020 Location: Australia Phase 1/2

(Continued)

Participants	Randomised: 150 participants **Inclusion criteria** • Male or female aged greater than or equal to 18 years • Confirmed SARS-CoV-2 by PCR with sample taken within 14 days prior to randomisation • Requirement for invasive or non-invasive ventilatory support or admission to ICU (or planned commencement of invasive or non-invasive ventilatory support, or planned admission to ICU) • Enrolled prior to or within 24 hours of ICU admission **Exclusion criteria** • Absolute neutrophil count less than 0.5 x 10e9/Litre, platelets less than 50 x 10e9/Litre • Previous TNFa antagonist treatment within the last 3 months • Confirmed bacterial sepsis or untreated bacterial, mycobacterial or fungal infection • Untreated hepatitis B virus infection • Recent major surgery within the last 8 weeks • Organ transplant recipients • Primary or secondary immunodeficiency • History of diverticulitis, inflammatory bowel disease, or other symptomatic gastrointestinal condition that might predispose to bowel perforation • Known cirrhosis or aminotransferases greater than 5 times upper limit of normal • Pregnant or breastfeeding • Known allergy or hypersensitivity to TCZ or other monoclonal antibodies • Previous participation in the trial • Patient being treated with palliative intent, or not expected to be alive in 48 hours
Interventions	**Intervention:** tocilizumab (IV, 400 mg, single dose) **Control intervention:** standard of care
Outcomes	**Primary outcome** **Secondary outcomes** • Mortality (daily up to day 29) • Adverse events (daily up to day 29)
Starting date	Study start date: 19 October 2020
Contact information	QIMR Berghofer Medical Research Institute, Bridget Barber, +61733620104, bridget.barber@qimrberghofer.edu.au
Notes	Registered but not recruiting

CTRI/2020/12/029793	
Trial name or title	Efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia on steroid therapy: a prospective, randomized, double blind placebo-controlled trial
Methods	RCT, placebo-controlled, blind-label study Date of study: December 2020

(Continued)

	Location: India Phase 3
Participants	Randomised: 54 participants **Inclusion criteria** • Patients 18 years or older • Diagnosis of SARS-CoV-2 infection by RT-PCR • Pulmonary infiltrates on CXR/ CECT Chest • On COVID specific steroid therapy with IV methyl prednisolone 1 mg/kg/day or dexamethasone 6 mg per day • Severe respiratory failure with PaO_2 / FiO_2 less than 150 mmHg and IL-6 > 50 pg/mL with CRP > 50 mg/L • Signature of informed consent by the patient, family member or legal representative **Exclusion criteria** • Less than 24 hours of initiation of steroid therapy • Liver injury or failure (AST/ALT ≥ 5 x upper limit of normal) • Leukocytes < 2 × 103/µl • Thrombocytes < 50 × 103/µl • Severe bacterial infection (procalcitonin > 3ng/mL) • Acute or chronic diverticulitis • Immunosuppressive therapy (e.g. mycophenolate, azathioprine, methotrexate and biologicals) • Known active or chronic tuberculosis • Known active or chronic viral hepatitis • Known allergic reactions to tocilizumab or its ingredients
Interventions	**Intervention:** tocilizumab (IV, single dose, 8 mg/kg body weight) **Control interventions:** placebo
Outcomes	**Primary outcome** **Secondary outcomes** • Mortality (28 days) • Time to clinical improvement (28 days) • Change of ventilation mode and invasiveness · Change of ventilation mode and invasiveness
Starting date	Study start date: 31 December 2020
Contact information	Nehru Hospital, Naveen Naik, navin_amc@yahoo.com
Notes	Registered but not recruiting

ALT: alanine aminotransferase; **ANC**: absolute neutrophil count; **anti-HCV**: HCV antibody test; **ARD**S: acute respiratory distress syndrome; **AST**: aspartate aminotransferase; **BAL:** bronchoalveolar lavage;**BCRSS**: Brescia COVID respiratory severity score; **BP: blood pressure; CECT**: contrast enhanced computerised tomography; **CCL**: creatinine clearance; **COPD**: chronic obstructive pulmonary disease; **cPAP**: continuous positive airway pressure; **CRP**: C-reactive protein; **CURB-65**: also known as the CURB criteria (clinical prediction rule); **CT**: computerised tomography; **CXR**: chest radiograph; **DD:** D-Dimer; **DMARDs:** disease modifying antirheumatic drugs; **ECMO**: extracorporeal membrane oxygenation**; eGFR:** estimated glomerular filtration rate; **EUA**: emergency use authorisation; **FDA**: Food and Drug Agency; **GI**: gastro intestinal; **HBV**: hepatitis B; **HCV**: hepatitis C; **Hgb:** haemoglobin; **IC:** inclusion criteria; **ICU**: intensive care unit;**IL**: interleukin;

IP: investigational product; **IUD**: intrauterine device; **IUS**: intrauterine hormone-releasing system; **IV**: intravenous; **JAKi**: Janus kinase inhibitors; **L: litre; LAR:** legally acceptable representative; **LDH**: **lactate dehydrogenase**; **LSN**: lymphocyte:segmented **neutrophils; MEWS**: modified early warning score; **MTX**: methotrexate; **NYHA: New York Heart Association; NIV: non invasive ventilation; NS: normal saline; NYU: New York University; PCR**: polymerase chain reaction; **PEEP**: **positive end-expiratory pressure; PPD**: purified protein derivative; **qSOFA**: quick sequential organ failure assessment score; **RCT**: randomised controlled trial; **RNA**: ribonucleic acid; **RT-PCR**: real time polymerase chain reaction; **SARS**: severe acute respiratory syndrome; **SARS-CoV-2**: severe acute respiratory syndrome coronavirus 2; **SBP:** systolic blood pressure; **SC:** sub cutaneous; **SGOT:** serum glutamic-oxaloacetic transaminase; **SGPT**: serum glutamic pyruvic transaminase; **TB**: tuberculosis; **TCZ**: tocilizumab; **TNF**: tumour necrosis factor; **TNFα:** tumour necrosis factor alpha; **ULN:** upper limit of normal; US: ultra sound; **WBC:** white blood count;**WHO**: World Health Organization

Appendix 5. Details on the request to authors of unpublished trials

(i.e. Update on the status of the study: If ongoing, communicate the expected completion date; If complete, request to share results before publications) for information sent to investigators of IL 6-blocking agent trials registered.

Study ID	Trialist's contact name	Treatment	Date of contact	Reply (last check 28 January 2021)
EUC-TR2020-001275-32-DK / NCT04322773	Dr Lars Erik Kristensen	Sarilumab/ Tocilizumab	3 Nov 2020	No response
NCT04333914	Dr Virginie Avrillon	Tocilizumab	3 Nov 2020	Cancelled
NL8504	Dr Margriet Dijkstra	Tocilizumab	3 Nov 2020	No response
NCT04335071	Dr Peter M. Villiger	Tocilizumab	3 Nov 2020	Stopped Couldn't include a sufficient number of patients
NCT04361552	Dr Ajay K Nooka	Tocilizumab	3 Nov 2020	Cancelled
EUC-TR2020-001408-41-DE	Dr Tobias Wengenmayer	Tocilizumab	3 Nov 2020	Stopped
EUC-TR2020-001770-30-BE	Dr Camelia Rossi	Tocilizumab	3 Nov 2020	No response
NCT04377750	Dr.Juli Benbenisty	Tocilizumab	3 Nov 2020	Required further details – willing to collaborate
IRC-T20200510047383N1	Dr Mohammadreza Bo-zorgmanesh	Tocilizumab	3 Nov 2020	No response
AC-TRN12620000580976	Prof Bridget Barber	Tocilizumab	3 Nov 2020	Not started yet Lack of patients in Australia
NCT04412291	Dr Jon Lampa	Tocilizumab	3 Nov 2020	Recruiting The expected completion date is December 2021
NCT04412772	Dr Todd Seto	Tocilizumab	3 Nov 2020	No response
NCT04435717	Dr Jose A Perez-Molina	Tocilizumab	3 Nov 2020	Stopped Will share data on included patients

(Continued)

CTRI/2020/05/025369	Dr Pooja Sharma	Tocilizumab	3 Nov 2020	No response
IRC-T20081027001411N4	Dr Mahdi Mahmoudi	Tocilizumab	3 Nov 2020	No response
NCT04479358	Dr Pankti D Reid	Tocilizumab	3 Nov 2020	Completed
IRC-T20200525047570N1	Dr Negin Hadisi	Tocilizumab	3 Nov 2020	Completed
NCT04577534	Dr Jarmo Oksi	Tocilizumab	3 Nov 2020	Ongoing The expected completion date is in 2 to 3 months.
EUC-TR2020-001767-86-IE	University College Dublin - QRAM	Tocilizumab	3 Nov 2020	No response
NCT04690920	Arif Malik	Tocilizumab	3 Nov 2020	No response
CTRI/2020/12/029793	Naveen Naik B	Tocilizumab	3 Nov 2020	No response
NCT04315298	Regeneron Pharmaceuticals	Sarilumab	3 Nov 2020	Required further details
EUC-TR-2020-001246-18-FR	Dr Cécile Kedzia	Sarilumab/ Tocilizumab	3 Nov 2020	No response
NCT04345289	Dr Thomas Benfield	Sarilumab	3 Nov 2020	Stopped
NCT04357808	Dr Rosario Garcia de Vicuña	Sarilumab	3 Nov 2020	Ongoing The expected completion date is December 2020
NCT04357860	Dr Julián de la Torre Cisneros	Sarilumab	03/11/2020	Ongoing The expected completion date is in 6 to 7 months.
NCT04359901	Dr Westyn Branch-Elliman	Sarilumab	3 Nov 2020	Ongoing The expected completion date is not provided
EUC-TR2020-002037-15-ES	Dr Belen Ruiz Antorán	Sarilumab	3 Nov 2020	Recruiting The expected completion date is January 2021.
EUC-TR2020-001390-76-IT	Dr Giovanna Onnelli	Sarilumab	3 Nov 2020	Ongoing The expected completion date is May to June 2021.
EUC-TR2020-001290-74-ES	Dr Ana Aldea	Sarilumab	3 Nov 2020	No response

(Continued)

NCT04351724	Dr Bernd Jilma	Clazakizumab	3 Nov 2020	Cancelled
NCT04343989	Dr Bonnie Lonze	Clazakizumab	3 Nov 2020	No response
NCT04348500	Dr Noriko Ammerman	Clazakizumab	9 Nov 2020	No response
NCT04363502	Dr Nada Alachkar	Clazakizumab	3 Nov 2020	No response
NCT04381052	Dr David J. Cohen	Clazakizumab	3 Nov 2020	No response
NCT04494724	Dr Isioma Agboli	Clazakizumab	3 Nov 2020	No response
NCT04659772	Dr Ayan Sen	Clazakizumab	26 Jan2021	No response
NCT04380519	Dr Mikhail Samsonov	Olokizumab	20 Nov 2020	No response
NCT04452474	Dr Mikhail Samsonov	Olokizumab	3 Nov 2020	No response
NCT04397562	Biocad	Levilimab	Not yet contacted	No correspondence email
NCT04330638	Dr Bart Lambrecht	Siltuximab/ Tocilizumab	1 Dec 2020	No response

Appendix 6. Details on the request for information sent to authors of published IL 6-blocking agent trials

Study ID	Author's contact name	Treatment	Requested information	Date of contact	Reply (last check 27/01/2021)
Rosas COVACTA 2021	Dr Ivan O. Rosas	Tocilizumab	Study's protocol and statistical plan + some missing data for: outcomes, co-interventions, participant characteristics	25 Sep 2020	Missing data requested received on 7 December 2020. Protocol and statistical plan still not available.
Wang 2020	Drs Xiaoling Xu and Xiaodong Mei	Tocilizumab	Study's protocol and statistical plan +some missing data for: outcomes, co-interventions, participant characteristics	25 Sep 2020	Cannot share before publication
Hermine CORIMUNO-19 2020	Dr Xavier Mariette	Tocilizumab	Request to share all required data	9 Oct 2020	Publication received+ all requested data 23 October 2020
Salvarani 2020	Dr Carlo Salvarani	Tocilizumab	Some missing data for: outcomes, co-interventions, participant characteristics	3 Nov 2020	No response
Stone 2020	Dr Stone	Tocilizumab	Some missing data for: outcomes, co-interventions, participant characteristics	3 Nov 2020	No response

(Continued)

Salama EMPACTA 2020	Dr Shalini V. Mohan	Tocilizumab	Study's protocol and statistical plan + some missing data for: Outcomes, Co-interventions, Participant characteristics	3 Nov 2020	e-mail received with some of the data requested on 3 Dec 2020
Gordon REMAP-CAP 2021	Dr Anthony Gordon	Sarilumab Tocilizumab	Some missing data for: outcomes, co-interventions, participant characteristics	25 Jan 2021	No response
Veiga TOCIBRAS 2021	1. Viviane C Veiga	Tocilizumab	Some missing data for: outcomes, co-interventions, participant characteristics	1 Feb 2021	
Lescure 2021	2. Dr Francois X Lescure	Sarilumab	Some missing data for: outcomes, co-interventions, participant characteristics	12 Feb 2021	No response
Horby RECOVERY 2021	Professor Peter W Horby and Professor Martin J Landray	Tocilizumab	*	*	Not yet contacted

Appendix 7. Matrices indicating availability of trial results for critical and important outcomes

Appendix 7.1 Matrix indicating availability of trial results for the critical and important outcomes of the review. Tocilizumab versus standard care/placebo

Appendix 7.1.1 Matrix indicating availability of trial results for the critical outcomes of the review. Tocilizumab versus standard care/placebo

				Critical outcomes							
Trial ID	**Study follow-up (in days)**	**TZ n**	**Standard of care or Placebo n**	**All-cause mortality**		**Clinical improvement**		**WHO SCORE 7 and above**		**AE**	**SAE**
				Day 28	**Day ≥60**	**Day 28**	**Day ≥60**	**Day 28**	**Day ≥60**		
Rosas COVACTA 2021	60	301	151	✓	*	*	*	✓	*	✓	✓
Wang 2020	14	33	32	X	*	*	*	✓	*	✓	✓
Hermine CORIMUNO-19 2020	90	64	67	✓	✓	✓	*	✓	*	✓	✓
Salvarani 2020	30	60	66	✓	*	✓	*	*	*	✓	✓
Stone 2020	28	161	82	✓	*	✓	*	*	*	✓	✓
Salama EMPACTA 2020	60	259	129	✓	✓	*	*	*	*	✓	✓
Gordon REMAP-CAP 2021	90	48	412	✓	*	*	*	*	*	*	✓
Horby RECOVERY 2021	28	2022	2094	✓	*	✓	*	✓	*	*	*

Key:
✓ A study result is available for inclusion in the synthesis
X No study result is available for inclusion, (probably) because the P value, magnitude or direction of the results generated were considered unfavourable by the study investigators
– No study result is available for inclusion, (probably) because the outcome was not assessed, or for a reason unrelated to the P value, magnitude or direction of the results
? No study result is available for inclusion, and it is unclear if the outcome was assessed in the study

AE: adverse event; **SAE**: serious adverse event; **TZ**: tocilizumab

Appendix 7.1.2 Matrix indicating availability of trial results for important outcomes of the review: tocilizumab versus standard care/ placebo

				Important outcomes		
Trial ID	Study follow-up (in days)	Sample size Tocilizumab	Sample size Standard of care or Placebo	**Time to death**	**Time to clinical improvement**	**Time to WHO score 7 and above**
Rosas COVACTA 2021	60	301	151	*	✓	*
Wang 2020	14	33	32	*	*	*
Hermine CORIMUNO-19 2020	90	64	67	✓	✓	✓
Salvarani 2020	30	60	66	*	✓	*
Stone 2020	28	161	82	✓	✓	✓
Salama EMPACTA 2020	60	259	129	✓	✓	*
Gordon REMAP-CAP 2021	90	366	412	✓	✓	*
Horby RECOVERY 2021	28	2022	2094	*	*	*

Key:
✓ A study result is available for inclusion in the synthesis
X No study result is available for inclusion, (probably) because the P value, magnitude or direction of the results generated were considered unfavourable by the study investigators
– No study result is available for inclusion, (probably) because the outcome was not assessed, or for a reason unrelated to the P value, magnitude or direction of the results
? No study result is available for inclusion, and it is unclear if the outcome was assessed in the study

AE: adverse event; **SAE**: serious adverse event; **TZ**: tocilizumab

Appendix 7.2. Matrix indicating availability of trial results for the critical and important outcomes of the review: sarilumab

Appendix 7.2.1 Matrix indicating availability of trial results for the critical outcomes of the review: sarilumab 400 mg versus standard care

				Critical outcomes							
Trial ID	**Study follow-up (in days)**	**SAR 400 mg n**	**Standard of care or Placebo n**	**All-cause mortality**		**Clinical improvement**		**WHO SCORE 7 and above**		**AE**	**SAE**
				Day 28	**Day ≥60**	**Day 28**	**Day ≥60**	**Day 28**	**Day ≥60**		
Gordon REMAP-CAP 2021	90	48	412	✓	*	*	*	*	*	*	✓
Lescure 2021	60	173	86	✓	✓	X	*	*	*	✓	✓

AE: adverse event; **SAE**: serious adverse event; **SAR**: sarilumab

Appendix 7.2.2 Matrix indicating availability of trial results for important outcomes of the review. Sarilumab 400 mg versus standard care

				Important outcomes		
Trial ID	Study follow-up (in days)	Sample size Sarilumab 400 mg	Sample size Standard of care or Placebo	**Time to death**	**Time to clinical improvement**	**Time to WHO score 7 and above**
Gordon REMAP-CAP 2021	90	48	412	✓	✓	*
Lescure 2021	60	173	86	*	✓	*

Key:
✓ A study result is available for inclusion in the synthesis
X No study result is available for inclusion, (probably) because the P value, magnitude or direction of the results generated were considered unfavourable by the study investigators
– No study result is available for inclusion, (probably) because the outcome was not assessed, or for a reason unrelated to the P value, magnitude or direction of the results
? No study result is available for inclusion, and it is unclear if the outcome was assessed in the study

Appendix 7.2.3 Matrix indicating availability of trial results for the critical outcomes of the review: sarilumab 200 mg vs standard care

				Critical outcomes							
Trial ID	**Study follow-up (in days)**	**SAR 200 mg n**	**Standard of care or Placebo n**	**All-cause mortality**		**Clinical improvement**		**WHO SCORE 7 and above**		**AE**	**SAE**
				Day 28	**Day ≥60**	**Day 28**	**Day ≥60**	**Day 28**	**Day ≥60**		
Lescure 2021	60	161	86	✓	✓	X	*	*	*	✓	✓

AE: adverse event; **SAE**: serious adverse event; **SAR**: sarilumab

Appendix 7.2.4 Matrix indicating availability of trial results for important outcomes of the review: sarilumab 200 mg vs standard care

				Important outcomes		
Trial ID	Study follow-up (in days)	Sample size Sarilumab 200 mg	Sample size Standard of care or Placebo	**Time to death**	**Time to clinical improvement**	**Time to WHO score 7 and above**
Lescure 2021	60	161	86	*	✓	*

Key:
✓ A study result is available for inclusion in the synthesis
X No study result is available for inclusion, (probably) because the P value, magnitude or direction of the results generated were considered unfavourable by the study investigators
– No study result is available for inclusion, (probably) because the outcome was not assessed, or for a reason unrelated to the P value, magnitude or direction of the results
? No study result is available for inclusion, and it is unclear if the outcome was assessed in the study

Appendix 8. Table of results for tocilizumab versus placebo or standard care: important outcomes.

Outcome	No. of studies	No. of participants	Statistical method	Effect size
Time to clinical improvement	6	2118	Hazard Ratio (95% CI)	1.23 (1.08 to 1.39)
Time to WHO progression score (level 7 and above)	3	762	Hazard Ratio (95% CI)	0.62 (0.42 to 0.91)
Time to death	3	1152	Hazard Ratio (95% CI)	0.65 (0.51 to 0.83)

Appendix 9. Table of results for sarilumab versus placebo or standard care: important outcomes.

Outcome	No. of studies	No. of participants	Statistical method	Effect size
Time to clinical improvement	2	880	Hazard Ratio (95% CI)	1.28 (0.88 to 1.87)
Time to death	1	460	Hazard Ratio (95% CI)	0.55 (0.33 to 0.91)

Appendix 10. Affiliations of the COVID-NMA consortium's participating members

Affiliations of the COVID-NMA consortium's participating members listed in the Acknowledgment section

(See Acknowledgements)

1. Université de Paris, France
2. Centre of Research in Epidemiology and StatisticS (CRESS UMR1153), Methods team, France
3. Laboratoire d'Informatique de Grenoble (LIG), CNRS, France
4. IRCCS Fondazione Don Carlo Gnocchi, Italy
5. Laboratoire Bordelais de Recherche en Informatique (LaBRI), Université Bordeaux I, France
6. Epistemonikos Foundation, Chile
7. McMaster University, Canada
8. Center for Health Regulatory Policies, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Italy
9. Centre Max Weber, CNRS, France
10. Centre of Research in Epidemiology and StatisticS (CRESS UMR1153), Eren team, France
11. Cochrane Response
12. Cochrane Germany, Cochrane Germany Foundation, Freiburg, Germany
13. Bordeaux Pharmacoepi - ADERA, France
14. Laboratoire d'Informatique, de Modélisation et d'Optimisation des Systèmes (LIMOS), CNRS, Université Clermont Auvergne
15. Université Toulouse 3 – Paul Sabatier - Institut de Recherche en Informatique de Toulouse – IRIT UMR 5505, France
16. Cochrane France
17. Institut des Systèmes Complexes de Paris IDF (ISC-PIF), CNRS, France
18. WHO Collaborating Centre for Guideline Implementation and Knowledge Translation & Chinese GRADE Centre, Lanzhou University, China
19. Laboratoire de recherche en Informatique (LRI), CNRS, Université Paris-Saclay, France
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22. Centre for Evidence Based Medicine Odense (CEBMO), University of Southern Denmark and Odense University Hospital, Denmark
23. French National Research Institute for Agriculture, Food and Environment (INRAE), France
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32. Research Methodology Division, School of Public Health and Preventive Medicine, Monash University, Australia
33. Health Research Board-Trials Methodology Research Network (HRB-TMRN), NUI Galway, Ireland
34. UC Evidence Center, Cochrane Chile Associated Center, Pontificia Universidad Católica de Chile, Santiago, Chile
35. Population Health Sciences, Bristol Medical School, University of Bristol, UK; NIHR CLAHRC West, University Hospitals Bristol and Weston NHS Foundation Trust, UK
36. Bristol Medical School, Bristol Population Health Science Institute, University of Bristol, UK
37. Nottingham Ningbo GRADE Centre, The Nottingham China Health Institute, the University of Nottingham Ningbo, China
38. Laboratoire d'Informatique pour la Mécanique et les Sciences de l'Ingénieur (LIMSI), CNRS, France

Appendix 11. 'Risk of bias' assessments

Clinical improvement (D28)

Study	1.Randomisation	2.Deviations from intervention	3.Missing outcome data	4.Measurement of the outcome	5.Selection of the reported results	Overall risk of bias

(Continued)

Hermine 2020	Low	**Some concerns[1]**	Low	**Some concerns[2]**	Low	**Some concerns**
Rosas 2021	Low	Low	Low	Low	Low	Low
Salama 2020	Low	Low	Low	Low	Low	Low
Salvarani 2020	Low	**Some concerns[3]**	Low	**Some concerns[4]**	**Some concerns[5]**	**Some concerns**
Stone 2020	Low	Low	Low	Low	Low	Low
Horby 2021	Low	Low	Low	**Some concerns[6]**	Low	**Some concerns**
Veiga 2021	Low	**Some concerns[7]**	Low	**Some concerns[8]**	Low	**Some concerns**

[1] Quote: “Open-label study” Comment: unblinded study. Deviations from intended intervention arising because of the study context: three participants in the treatment group did not receive study drug. Administration of co-interventions of interest (antivirals, corticosteroids and biologics) were reported. The proportions of participants receiving antivirals and steroids were imbalanced between two arms (> 10% solute difference between the two arms) for steroids. This deviation could affect the outcome and was not balanced. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

2Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of clinical improvement probably does not differ between groups. Unblinded study. Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

3 Quote: "the trial was open label" Comment: unblinded study. Deviations from intended intervention arising because of the study context: cross over: 15 (23%) participants in the standard care arm received the study treatment. For 12 (18%) the studied treatment was administered because of clinical worsening as planned in the protocol. Nevertheless, this decision could have been influenced by the trial context. Administration of co-interventions of interest were reported and not balanced: antivirals (35% vs 47%) and corticosteroids (10% vs 10.6%). These deviations could affect the outcome. Nevertheless, this domain was rated as 'Some Concern' as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

4 Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of clinical improvement probably does not differ between groups. Unblinded study. Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

5 Comment: the protocol and statistical analysis plan were available. The outcomes 'Clinical improvement (defined as discharge)' is not present in the protocol or registry. No information on whether the results for these outcomes were selected from multiple outcome measurements or analyses of the data.

6Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of clinical improvement probably does not differ between groups. Unblinded study. Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

7 Quote: “open label” trial. Comment: unblinded study. Deviations from intended intervention arising because of the study context: cross over: 2/64 (3%) of the control arm received tocilizumab. Co-interventions of interest (corticosteroids and antivirals), were reported, but no information on another co-intervention of interest: biologics. Hence, this domain was rated as some concern as not enough information on deviations that arose because of the trial context were reported. Data for the outcome were analysed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.

8 Comment: method of measuring the outcome probably appropriate. Measurement or ascertainment of clinical improvement probably does not differ between groups. Unblinded study. Assessment of this outcome requires clinical judgement and can be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.

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WHAT'S NEW

Date	Event	Description
18 March 2021	Amended	Reporting of results for the outcome of time to clinical improvement and time to WHO clinical progression score (level 7 or above) amended in 'Effects of intervention'

HISTORY

Review first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

All authors contributed to the development of the review.

DECLARATIONS OF INTEREST

Lina Ghosn has no interest to declare.

Anna Chaimani has no interest to declare.

Theodoros Evrenoglou has no interest to declare.

Mauricia Davidson has no interest to declare.

Carolina Graña has no interest to declare.

Christine Schmucker has no interest to declare.

Claudia Bollig has no interest to declare.

Nicholas Henschke has been an employee of Cochrane Response since 2016. Cochrane Response was commissioned by the WHO to perform parts of this systematic review.

Yanina Sguassero been an employee of Cochrane Response since 2019. Cochrane Response was commissioned by the WHO to undertake tasks relevant to this systematic review.

Camilla Hansen Nejstgaard has no interest to declare.

Sonia Menon works as a systematic reviewer for p95 consultancy company.

Thu Van Nguyen has no interest to declare.

Gabriel Ferrand has no interest to declare.

Philip Kapp has no interest to declare.

Carolina Riveros has no interest to declare.

Camila Ávila has no interest to declare.

Declan Devane is Principal Investigator for a grant from the Health Research Board (HRB, Ireland) and the Health and Social Care, Research and Development (HSC R&D) Division of the Public Health Agency in Northern Ireland to establish Evidence Synthesis Ireland within which Cochrane Ireland is hosted. The funds are received by his institution. Declan's position as Director of Cochrane Ireland and Director of Cochrane Ireland is paid 0.5FTE from this grant.

Joerg J Meerpohl has no interest to declare.

Gabriel Rada has no interest to declare.

Asbjørn Hróbjartsson has no interest to declare.

Giacomo Grasselli has received personal fees for lectures from Getinge, Fisher&Paykel, Draeger Medical, Biotest, Thermofisher and MSD; support for travel-meeting expenses from Biotest and Getinge (all outside the present work). I also received an unrestricted research grant from Fisher&Paykel (unrelated to the present work).

David Tovey is a paid editorial advisor to Cochrane France.

Philippe Ravaud is minority shareholder of INATO and SAVANA. He is also principal investigator of the CORIMUNO platform (funding: French Ministry of Health, Programme Hospitalier de Recherche Clinique [PHRC COVID-19-20-0143, PHRC COVID-19-20-0029], Foundation for Medical Research (FRM), AP-HP Foundation and the Reacting program).

Isabelle Boutron has no interest to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes, in the review, to the protocol (Boutron 2020b).

1. **Outcomes**: to avoid multiplicity, we reduced the number of outcomes. For the selected outcome domains, we now consider only two time points (D28 and ≥ D60). We no longer evaluate the outcome domain WHO Clinical Progression Score level 6 or above as IL-6 blocking agents as the definition used in the studies appears to be subject to variation due to local guidelines and resources. It is therefore an unreliable or inconsistent indicator when assessed across studies.
2. **'Risk of bias' assessment**: we did not consider anticoagulants as a relevant co-intervention for assessing risk of bias in the domain deviations from intervention after discussion with content experts.
3. **Subgroup analyses**: the subgroup analyses planned to explore age, sex, severity of the disease, comorbidity status and time after the beginning of the outbreak were not conducted because of the limited number of RCTs providing relevant data and the absence of variation across trials in some variables such as age and gender. We decided to conduct post-hoc subgroup analysis to explore the impact of the funding source (public or non-profit/mixed or private) and conflict of interests

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [therapeutic use]; Antibodies, Monoclonal, Humanized [adverse effects] [*therapeutic use]; Bias; COVID-19 [*drug therapy] [mortality]; Disease Progression; Interleukin-6 [*antagonists & inhibitors]; Multicenter Studies as Topic; Randomized Controlled Trials as Topic

MeSH check words

Aged; Female; Humans; Male; Middle Aged