NICE National Institute for Health and Care Excellence

Tocilizumab for COVID-19

Evidence review

15 January 2021, last updated 24 February 2021

This evidence review was developed in January 2021 to support the NHS England Clinical Commissioning Policy. NICE has conducted a more recent review of the evidence for its COVID-19 guidance.

This evidence review sets out the best available evidence on tocilizumab for treating COVID-19. It should be read with the evidence summary, which gives the likely place in therapy and factors for decision making.

Commissioned by NHS England.

Disclaimer

The content of this evidence review was up to date in February 2021. New evidence may have been published since then. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date prescribing information.

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Background

COVID-19 is a disease caused by a novel coronavirus that emerged in Wuhan, China in December 2019. Other diseases caused by coronaviruses include severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the common cold. COVID-19 manifests as a respiratory illness, of widely varying clinical severity. At the most severe end of the spectrum, it results in severe pneumonia and respiratory failure. Acute respiratory distress syndrome (ARDS) is often the preterminal event in patients with COVID-19. Severe COVID-19 is often associated with release of proinflammatory cytokines, which may cause or exacerbate lung injury leading to life-threatening disease.

As of 21 February 2021, the World Health Organization COVID-19 dashboard reports 110,749,023 confirmed cases of COVID-19, with 4,105,679 confirmed cases and 120,365 deaths in the UK.

Intervention

Tocilizumab is a recombinant humanised monoclonal antibody belonging to the immunoglobulin G1 (IgG1) class. This is directed against the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor. IL-6 is a proinflammatory cytokine that is a key driver behind the cytokine-release syndrome seen in patients with severe COVID-19. By targeting IL-6 receptors, tocilizumab may mitigate the cytokine-release syndrome and prevent progression of disease. Tocilizumab has marketing authorisations for use in rheumatoid arthritis and giant cell arteritis in adults, systemic juvenile idiopathic arthritis and juvenile idiopathic polyarthritis in children 2 years and older, and chimeric antigen receptor T cell-induced severe or life-threatening cytokine-release syndrome in adults, young people and children 2 years and older (summaries of product characteristics for tocilizumab).

The marketing authorisations for tocilizumab do not cover use in COVID-19. This use is therefore off label, and the prescriber should follow relevant professional guidance and take full responsibility for the decision. See the General Medical Council's good practice in prescribing and managing medicines and devices for further information.

The dosage of tocilizumab used for COVID-19 has varied, but intravenous dosing of 8 mg/kg of body weight (up to a maximum of 800 mg) given once or twice, around 12 hours apart, has been used. Tocilizumab has been given subcutaneously for COVID-19, but this evidence review only considers intravenous use.

The most commonly reported adverse drug reactions with tocilizumab are upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased liver transaminases. See the summaries of product characteristics for tocilizumab for contraindications and cautions.

Clinical problem

The UK and Europe are currently experiencing a second wave of COVID-19, with the peak of the first wave having occurred in April 2020 in the UK. Initial UK hospital data suggest that increasing age over 50 years is a strong predictor of mortality in hospital (hazard ratio 2.6 for 50 to 59 years, 5.0 for 60 to 69 years, 8.5 for 70 to 79 years and 11.1 for 80 years and over, Docherty et al. 2020). There is UK primary care record data from 17.3 million patients linked to 10,926 COVID-19-related deaths in hospital. These showed that mortality was strongly associated with male gender, greater age, black or South Asian ethnicity, deprivation, obesity, diabetes, and cardiovascular and respiratory comorbidities (Williamson et al. 2020). The Chinese Centre for Disease Control and Prevention reported that cardiovascular disease, hypertension, diabetes, respiratory disease and cancers are risk factors for mortality (Deng et al. 2020). Children and young people appear to be less affected by the virus, with low numbers of deaths and critical care admissions in this age group (Lu et al. 2020).

Between 1 March and 31 August 2020, the Intensive Care National Audit Research Centre was notified of 10,904 patients who were admitted to critical care with COVID-19 in England, Wales and Northern Ireland. From 1 September to 4 December 2020, there have been a further 6,388 patients with confirmed COVID-19 admitted to critical care in these areas, with daily admissions showing an upward trend.

Objective

This evidence review aims to review the best available evidence on the effectiveness and safety of tocilizumab in adults and children hospitalised with moderate, severe or critical, suspected or confirmed COVID-19.

Review questions

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NHS England for the topic (see appendix A for more information). The review questions for this evidence review are:

1. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the clinical effectiveness of tocilizumab compared with placebo or standard care?

2. In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the safety of tocilizumab compared with placebo or standard care?

3. From the evidence selected, are there any subgroups of patients who may benefit (or be harmed) from tocilizumab more than the wider population of interest?

4. From the evidence selected, what dose or regimen of tocilizumab did patients receive?

5. From the evidence selected, which treatments had patients received as standard care?

Summary of included studies

A literature search for tocilizumab identified 1,081 references (see appendix E for full details). These references were screened using their titles and abstracts, and 39 full-text references were obtained and assessed for relevance.

Five published studies are included in this evidence review, together with prepublication study results from the nationally prioritised platform studies, Gordon et al. (2021; REMAP-CAP; study NCT02735707) and Horby et al. (2021; RECOVERY,

study NCT04381936). A summary of the included studies is shown in appendix B. Quality assessment of the included studies is in appendix C.

Horby et al. (2021) included 4,116 adults hospitalised with severe COVID-19, who had clinical evidence of progressive disease (hypoxia [oxygen saturation less than 92% on room air or receiving oxygen therapy] and systemic inflammation [C-reactive protein, CRP, of 75 mg/litre or more]; 55% receiving non-invasive or mechanical ventilation). Gordon et al. (2021) included 778 critically ill adults with severe COVID-19 receiving respiratory or cardiovascular organ support in an intensive care setting (72% receiving non-invasive or mechanical ventilation). Patients were randomised to tocilizumab or standard care within 24 hours of starting organ support.

The 5 published randomised controlled trials (RCTs) were in adults who were hospitalised with COVID-19 pneumonia. In Salama et al. (2021; EMPACTA, n=389), Salvarani et al. (2021; RCT-TCZ-COVID-19, n=126), and Stone et al. (2020; BACC Bay Tocilizumab Trial, n=243), patients had severe COVID-19 but were not receiving non-invasive or mechanical ventilation at baseline. In Hermine et al. (2021; CORIMUNO-TOCI, n=131), patients had moderate or severe disease but were not receiving non-invasive or mechanical ventilation and were not in intensive care. In Veiga et al. (2021; TOCIBRAS, n=129), patients had severe or critical COVID-19, and some were receiving non-invasive or mechanical ventilation at baseline (48%).

Thirty-two studies were excluded, the details of which are in appendix F.

Effectiveness and safety

Full details of the results are in appendix D.

Review question 1: In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the clinical effectiveness of tocilizumab compared with placebo or standard care?

Mortality and ventilation

Horby et al. (2021) found that, in adults with clinical evidence of progressive COVID-19 (hypoxia and systemic inflammation), there was a statistically significant reduction in mortality at 28 days in the tocilizumab group (596/2022, 29%) compared

with the standard-care group (694/2094; 33%, rate ratio 0.86, 95% confidence interval [CI] 0.77 to 0.96, p=0.007). In people not receiving mechanical ventilation at baseline, there was a statistically significant reduction in the combined outcome of mechanical ventilation or death with tocilizumab (33%) compared with standard care (38%; risk ratio 0.85, 95% CI 0.78 to 0.93, p=0.0005). However, there was no statistically significant difference in the combined outcome of non-invasive or mechanical ventilation at 28 days between the tocilizumab and standard-care groups in people not receiving ventilation at baseline. In people receiving mechanical ventilation at baseline, there was no statistically significant difference in successfully stopping mechanical ventilation at 28 days between the tocilizumab and standard-care groups.

Gordon et al. (2021) found that, in adults who were critically ill with severe COVID-19 receiving respiratory or cardiovascular organ support in an intensive care setting (72% on non-invasive or mechanical ventilation), there were fewer in-hospital deaths in the tocilizumab group (98/350, 28.0%) compared with the standard-care group (142/397, 35.8%). There was a statistically significant improvement in hospital survival (median adjusted odds ratio [aOR] 1.64, 95% credible interval [CrI] 1.14 to 2.35, probability of superiority >99.6%) and 90-day survival (median aHR 1.59, 95% CrI 1.24 to 2.05, probability of superiority more than 99.9%) with tocilizumab compared with standard care.

Salama et al. (2021) found that, in adults with severe COVID-19 who did not need ventilation at baseline, there was a statistically significant decrease in the combined outcome of mechanical ventilation or death by day 28 with tocilizumab compared with placebo (hazard ratio [HR] 0.56, 95% CI 0.33 to 0.97, p=0.04). However, there was no statistically significant difference in mortality alone.

Salvarani et al. (2021) found that, in adults with severe COVID-19 not needing ventilation at baseline, there was no statistically significant difference in death at 14 days or 30 days with tocilizumab compared with standard care.

Stone et al. (2020) found that in adults with severe COVID-19 not needing ventilation at baseline, there was no statistically significant difference in the combined outcomes

of mechanical ventilation or death at 28 days, or intensive care admission or death at 28 days, with tocilizumab compared with placebo.

Hermine et al. (2021) found that, in adults with moderate to severe COVID-19 not needing ventilation at baseline, there was no statistically significant difference in the combined outcome of non-invasive ventilation, mechanical ventilation or death at 14 days with tocilizumab plus standard care compared with standard care. There was also no statistically significant difference in the combined outcomes of non-invasive ventilation, mechanical ventilation or death at day 4 (greater than 5 on the World Health Organization 10-point Clinical Progression Scale [WHO-CPS]), and in mechanical ventilation or death at 28 days.

Veiga et al. (2021) found that, in adults with severe or critical COVID-19 (some of whom needed ventilation at baseline), there was no statistically significant difference in the combined outcome of mechanical ventilation or death at 15 days with tocilizumab compared with standard care. However, there was a statistically significant increase in mortality alone at 15 days, with 11 (17%) deaths in the tocilizumab group compared with 2 (3%) in the standard-care group (OR 6.42, 95% CI 1.59 to 43.2). There was no statistically significant difference in the combined outcome of mechanical ventilation or death at 8 days or 29 days, or in deaths alone at 28 days.

Organ support

Horby et al. (2021) found that, in adults with clinical evidence of progressive COVID-19 (hypoxia and systemic inflammation), there was a statistically significant reduction in haemodialysis or haemofiltration at 28 days in the tocilizumab group compared with the standard-care group (5% compared with 7%, risk ratio 0.75, 95% CI 0.59 to 0.96, p=0.02).

Gordon et al. (2021) found that, in adults who were critically ill with severe COVID-19, the median number of days free of organ support up to 21 days was statistically significantly higher in the tocilizumab group compared with the standard-care group (10 days, interquartile range [IQR] -1 to 16 compared with 0 days, IQR -1 to 15; median aOR 1.64, 95% CrI 1.25 to 2.14, probability of superiority more than

99.9%). Days free of organ support includes death, where all deaths were assigned a value of -1.

The median number of days free of organ support in survivors up to 21 days was 14 (IQR 7 to 17) in the tocilizumab group and 13 (IQR 4 to 17) in the standard-care group. Organ support included respiratory and or cardiovascular support.

Veiga et al. (2021) found that, in adults with severe or critical COVID-19 (some of whom needed ventilation at baseline), there was no statistically significant difference between tocilizumab and standard care in ventilator-free days or time to independence from supplemental oxygen at 29 days.

Time to hospital discharge

Horby et al. (2021) found that, in adults with clinical evidence of progressive COVID-19 (hypoxia and systemic inflammation), there was a greater probability of discharge from hospital within 28 days in the tocilizumab group compared with the standard-care group (54% compared with 47%, rate ratio 1.22, 95% CI 1.12 to 1.34, p<0.0001).

Gordon et al. (2021) found that, in adults who were critically ill with severe COVID-19, there was a statistically significant improvement in time to hospital discharge at 90 days (median aOR 1.41, 95% CrI 1.18 to 1.70, probability of superiority more than 99.9%) and time to intensive care discharge (median aOR 1.42, 95% CrI 1.18 to 1.70, probability of superiority more than 99.9%) with tocilizumab compared with standard care.

Salama et al. (2021) and Salvarani et al. (2021) found that, in adults with severe COVID-19 not needing ventilation at baseline, there was no statistically significant difference in time to hospital discharge at 14 days or 30 days between tocilizumab and standard care (Salvarani et al. 2021), and at 28 days between tocilizumab and placebo (Salama et al. 2021).

Veiga et al. (2021) found that, in adults with severe or critical COVID-19 (some of whom needed ventilation at baseline), there was a statistically significant decrease in mean duration of hospital stay with tocilizumab compared with standard care (mean [standard deviation, SD] 11.3 [8.0] days and 14.7 [8.2] days respectively; rate ratio

0.70, 95% CI 0.55 to 0.87, p=0.001). In a post-hoc analysis of people who were discharged from hospital, length of hospital stay was also statistically significantly lower in the tocilizumab group compared with standard care.

Disease progression or change in clinical status

Gordon et al. (2021) found that, in adults who were critically ill with severe COVID-19, there was a statistically significant improvement in WHO ordinal scale at day 14 (median aOR 1.83, 95% CrI 1.40 to 2.41, probability of superiority more than 99.9%). In adults who were not intubated at baseline, statistically significantly fewer progressed to intubation, extracorporeal membrane oxygenation (ECMO) or death in the tocilizumab group (100/242, 41.3%) compared with the standard-care group (144/273, 52.7%; median aOR 1.69, 95% CrI 1.17 to 2.42, probability of superiority 99.8%).

Salama et al. (2021) found that, in adults with severe COVID-19 not needing ventilation at baseline, there was no statistically significant difference in median time to improvement in clinical status (7-category ordinal scale) between tocilizumab and placebo at 28 days.

Salvarani et al. (2021) found that, in adults with severe COVID-19 not needing ventilation at baseline, there was no statistically significant difference in clinical worsening at 14 days between the tocilizumab and standard-care groups. Clinical worsening was defined as admission to intensive care with mechanical ventilation, death or oxygen impairment (PaO_2/FIO_2 less than 150 mmHg).

Stone et al. (2020) found that in adults with severe COVID-19 not needing ventilation at baseline there was no statistically significant difference in time to clinical worsening (7-category ordinal scale) at 28 days between tocilizumab and placebo.

Hermine et al. (2021) found that, in adults with moderate to severe COVID-19 not needing ventilation at baseline, there was no statistically significant difference in clinical status (based on WHO-CPS) between tocilizumab and standard care at 7 days or 14 days.

Veiga et al. (2021) found that, in adults with severe or critical COVID-19 (some of whom needed ventilation at baseline), there was no statistically significant difference in clinical status at 8 or 29 days between tocilizumab and standard care.

Review question 2: In adults, young people and children hospitalised with suspected or confirmed COVID-19, what is the safety of tocilizumab compared with placebo or standard care?

Adverse events

Horby et al. (2021) reported 3 serious adverse reactions believed to be related to tocilizumab: otitis externa, *Staphylococcus aureus* bacteraemia, and lung abscess. All resolved with standard treatment. No statistical analysis was reported.

Stone et al. (2020) found a statistically significant increase in frequency of neutropenia but, counterintuitively, a decrease in serious infections in the tocilizumab group compared with the placebo group (13.7% compared with 1.2% [p=0.002] and 8.1% compared with 17.1% [p=0.03], respectively).

There were no statistically significant differences reported in other adverse events or serious adverse events between tocilizumab and placebo or standard care in any of the other included studies. However, most studies only had a 1-month follow-up period so longer-term safety outcomes of tocilizumab were not assessed.

See the summaries of product characteristics for tocilizumab for contraindications, cautions and a general summary of the safety profile.

Review question 3: From the evidence selected, are there any subgroups of patients that may benefit (or be harmed) from tocilizumab more than the wider population of interest?

Horby et al. (2021) reported prespecified subgroup analyses for the primary outcome of mortality at 28 days for subgroups of age, sex, ethnicity, level of respiratory support, days since symptom onset and use of corticosteroids (including dexamethasone). There was a statistically significant reduction in mortality in the tocilizumab group compared with the standard-care group in:

- men (rate ratio 0.81, 95% CI 0.71 to 0.93)

- people from a white family background (rate ratio 0.83, 95% CI 0.73 to 0.95)
- people with 7 days or fewer since symptom onset (rate ratio 0.81, 95% CI 0.67 to 0.97)
- people taking systemic corticosteroids (rate ratio 0.80, 95% CI 0.70 to 0.90).

There was no statistically significant difference in women, black, Asian or minority ethnic groups, people with more than 7 days since symptom onset, people not taking corticosteroids, or any of the other subgroups including age categories or respiratory support at randomisation. See appendix D for the full results.

Gordon et al. (2021) reported prespecified subgroup analyses by terciles of CRP, and similar effects were seen across all prespecified CRP subgroups.

Stone et al. (2020), Salama et al. (2020), and Veiga et al. (2021) found no statistically significant differences between tocilizumab and standard care in subgroup analyses including by age, sex, ethnicity, obesity, diabetes and concomitant treatment.

Review question 4: From the evidence selected, what dose or regimen of tocilizumab did patients receive?

Table 1 The dose and regimens of tocilizumab used in the included studies

Study	Tocilizumab dose and regimen
Gordon et al. 2021	Tocilizumab 8 mg/kg (maximum dose 800 mg) as an intravenous infusion over 1 hour, with the dose repeated at 12 to 24 hours at the discretion of the clinician
Hermine et al. 2021	Tocilizumab 8 mg/kg intravenously on day 1, with an additional dose of 400 mg intravenously on day 3 if oxygen requirement was not decreased by 50% and at the discretion of the clinician
Horby et al. 2021	Tocilizumab (by body weight bands: 800 mg if weight more than 90 kg, 600 mg if more than 65 kg to 90 kg or less, 400 mg if more than 40 kg to 65 kg or less, 8 mg/kg if 40 kg or less) intravenously. Second dose given after 12 to 24 hours at the discretion of the clinician if the patient's condition had not improved
Salama et al. 2021	Tocilizumab 8 mg/kg intravenously up to a maximum of 800 mg (1 or 2 doses), with the

	second dose given 8 to 24 hours after the first if status worsened or did not improve
Salvarani et al. 2021	Tocilizumab 8 mg/kg intravenously up to a maximum of 800 mg, followed by a second dose after 12 hours
Stone et al. 2020	Tocilizumab 8 mg/kg intravenously as a single dose (maximum dose 800 mg)
Veiga et al. 2021	Tocilizumab 8 mg/kg intravenously as a single dose (maximum dose 800 mg)

Review question 5: From the evidence selected, which treatments had patients received as standard care?

Table 2 The standard-care treatments used in the included studies

Study	Standard care
Gordon et al. 2021	Standard care included corticosteroids in most patients and remdesivir in about a third of patients
Hermine et al. 2021	Tocilizumab group: antivirals (11%), corticosteroids (33%), anticoagulants (94%), additional immunomodulator (2% anakinra) Standard-care group: antivirals (24%), corticosteroids (61%), anticoagulants (91%), additional immunomodulator (5% anakinra; 1%, eculizumab)
Horby et al. 2021	Tocilizumab group: corticosteroids (82%) Standard-care group: tocilizumab or sarilumab (3%), corticosteroids (82%)
Salama et al. 2021	Tocilizumab group: antivirals (79%), corticosteroids (80%) Placebo group: antivirals (79%), corticosteroids (88%)
Salvarani et al. 2021	Standard care following the protocols of each clinical centre until clinical worsening and then patients could have tocilizumab or standard care as a rescue therapy. Tocilizumab group: corticosteroids (8%) Standard-care group: tocilizumab (22%), corticosteroids (5%)

Stone et al. 2020	Tocilizumab group: remdesivir (33%), hydroxychloroquine (4%), corticosteroids (11%) Placebo group: remdesivir (29%), hydroxychloroquine (4%), corticosteroids (6%)
Veiga et al. 2021	Tocilizumab group: antibiotics (96%), antivirals (10%), corticosteroids (84%) Standard-care group: tocilizumab (3%), antibiotics (98%), antivirals (5%), corticosteroids (89%)

Limitations of the evidence

Horby et al. (2021; the RECOVERY study) investigated the use of tocilizumab in a broad range of people who were hospitalised with severe COVID-19. Patients had clinical evidence of progressive COVID-19, which was defined as hypoxia (oxygen saturation less than 92% on room air or receiving oxygen therapy) and systemic inflammation (C-reactive protein [CRP] 75 mg/litre or more). About 45% of patients received no ventilator support, 41% received non-invasive ventilation and 14% were mechanically ventilated. Results from this study substantially add to the evidence base for tocilizumab in COVID-19, with over 4,000 adults included in the study.

Gordon et al. (2021; the REMAP-CAP study) and Veiga et al. (2021) were the only other studies to include people receiving mechanical ventilation (30% and 16% respectively). In Gordon et al. (2021), patients were critically ill with severe COVID-19 and receiving organ support in an intensive care setting, and had to be enrolled within 24 hours of starting organ support. In Veiga et al. (2021), patients had severe or critical COVID-19 and receiving oxygen or mechanical ventilation (for less than 24 hours), and had at least 2 abnormal serum biomarkers.

Hermine et al. (2021) included people with moderate to severe COVID-19, and the other studies included people with severe COVID-19 (Salama et al. 2020, Salvarani et al. 2021, and Stone et al. 2020). The definition of severe COVID-19 differed between these studies. All 7 included studies allowed concomitant standard care in both groups.

Risk of bias was rated as either 'some concerns' (Gordon et al. 2021, Hermine et al. 2021, Horby et al. 2021, Salvarani et al. 2021 and Veiga et al. 2021) or 'low' (Stone et al. 2020 and Salama et al. 2020). Gordon et al. (2021), Hermine et al. (2021), Horby et al. (2021), Salvarani et al. (2021) and Veiga et al. (2021) were open label, so could have been subject to bias. However, a lack of blinding is unlikely to have affected the primary outcomes, for example, mortality or the need for organ support. The study by Veiga et al. (2021) was stopped early because of a higher mortality rate in the tocilizumab group. This may have contributed to the differences seen in baseline characteristics, which makes interpretation of the results difficult.

Gordon et al. (2021) and Horby et al. (2021) are nationally prioritised platform studies, but these data are preliminary, follow up is not complete, and the study results have not been peer reviewed. In Horby et al. (2021), data were missing for 8% of patients for the primary outcome at the time of reporting. Most patients (above 80%) received corticosteroids in these 2 studies, and both studies are highly applicable to UK practice in patients who are hospitalised with severe COVID-19.

Horby et al. (2021) reported prespecified subgroup analyses of the primary outcome (28-day mortality) defined by 6 baseline characteristics: age, sex, ethnicity, level of respiratory support, days since symptom onset and use of systemic corticosteroids (including dexamethasone). It is difficult to draw firm conclusions, because the results are based on multiple subgroup comparisons and any differences may be caused by chance. However, the analyses suggest that a mortality benefit was seen particularly in people receiving systemic corticosteroids, men, people from a white family background, and people with symptom onset in 7 days or less. This may have been because of larger numbers of people included in these subgroups. Although the risk of death was similar in men and women, there was no mortality benefit with tocilizumab compared with usual care in women only. Data from Horby et al. (2021) also suggest that tocilizumab may be less effective compared with usual care in people who are receiving mechanical ventilation at baseline. However, there are fewer data available in this group, and it is not clear how long after being mechanically ventilated people received tocilizumab. Gordon et al. (2021) reported prespecified subgroup analyses by terciles of CRP, and similar effects were seen across all prespecified CRP subgroups.

The dose of tocilizumab was 8 mg/kg intravenously in most studies. In Horby et al. (2021), the dose was determined by body weight (800 mg, 600 mg or 400 mg). The maximum dose was 800 mg in all studies. A second dose was given to everyone at 12 hours in Salvarani et al. (2021). A second dose was given based on clinical worsening and the discretion of the clinician at 3 days in Hermine et al. (2021), at 12 to 24 hours in Horby et al. (2021) and Gordon et al. (2021), and at 8 to 24 hours in Salama et al. (2020). A single dose was given in Stone et al. (2020) and Veiga et al. (2021). No subgroup analyses were reported for people who had a second dose because of clinical worsening, so it is not possible to say if this is more or less effective than a single dose.

Most studies had a 1-month follow-up period for the primary outcomes and some patients remained in hospital at the time of reporting. Therefore, the longer-term effects of tocilizumab in COVID-19 are not known.

All included studies were in adults, so it is not possible to say what the efficacy or safety of tocilizumab is in children or young people.

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Development of the evidence review

Process

The evidence summaries: process guide sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

Table 3 Details of expert advisers and any declarations of interest

Name, job title, organisation	Declaration of interests
Dr Daniele Bryden, consultant in intensive care medicine, Sheffield NHS Foundation Trust; vice dean, Faculty of Intensive Care Medicine	No direct interests
Dr James Watts, consultant in anaesthesia and critical care, East Lancashire Hospitals NHS Trust	No direct interests
Professor Mike Morgan, consultant respiratory physician, University Hospitals of Leicester NHS Trust (first version only)	No direct interests
Dr Natasha Ratnaraja, consultant in infection, University Hospitals Coventry and Warwickshire NHS Trust	No direct interests

Update information

24 February 2021: We updated the evidence summary at the request of NHS England because new evidence was identified: prepublication study results from the nationally prioritised platform study (Horby et al. 2021; the RECOVERY study), and a published randomised controlled trial (Veiga et al. 2021). See the summary of included studies for more information.

Appendices

Appendix A: PICO table

Population, Intervention, Comparator and Outcomes (PICO) table

Criteria	Details
Population and indication	Adults and children hospitalised with moderate, severe or critical suspected or confirmed COVID-19 (COVID-19 infection is the acute clinical syndrome caused by SARS-CoV2 virus) Subgroups: • adults over 50 years • children under 12 years • disease severity (moderate, severe or critical) • gender • ethnic background • pregnant women • comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • time from symptom onset.
Intervention	Tocilizumab delivered intravenously
Comparators	Placebo with standard-care or standard care alone. Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as dexamethasone, remdesivir).
Outcomes	Critical to decision making: • mortality • requirement for or duration of: – mechanical ventilation – non-invasive ventilation (continuous positive airway pressure, non-invasive ventilation or high-flow oxygen therapy) – organ support (extracorporeal membrane oxygenation, vasopressors, renal replacement treatment)

	• serious adverse events (grade 3 or 4). Important to decision making: • time to recovery or SARS-CoV-2 RT-PCR negativity • length of stay (hospital or critical care) • disease progression or change in clinical status, to include: – initiation of ventilation – transfer or admission to critical care • adverse events.
Inclusion criteria	-
Study design	Systematic reviews of randomised controlled trials and randomised controlled trials
Language	English
Patients	Human studies only
Age	All ages
Date limits	2019 to 2020
Exclusion criteria	-
Publication type	Preprints before peer review. Apart from: • peer-reviewed journal publications (including in-press, pre-proof or epub-ahead-of-print articles) or • prepublication study results that meet minimum dataset requirements from Department of Health and Social Care nationally prioritised platform studies, such as RECOVERY or REMAP-CAP.
Study design	Controlled clinical trials, observational studies including case series and case reports

The definitions of COVID-19 disease severity in adults are according to the WHO Clinical Management of COVID-19: interim guidance.

Appendix B: Summary of included studies

Summary of included studies table

Study	Number of patients	Population	Intervention	Comparison	Outcomes
Gordon et al. 2021 (REMAP-CAP, NCT02735707) Unpublished open-label randomised controlled trial Global, mainly UK	n=778	Adults critically ill with severe suspected or confirmed COVID-19 receiving respiratory or cardiovascular organ support in intensive care. Patients had to be enrolled within 24 hours of starting organ support. Baseline respiratory support: • None or supplemental oxygen only (0.4%). • High-flow nasal cannula (29.3%). • Non-invasive ventilation (41.9%). • Mechanical ventilation (29.8%). Patients were excluded when there was a presumption that death was imminent. Baseline median (IQR) CRP 150 mg/litre (85 to 221 mg/litre) in tocilizumab group and 130 mg/litre (71 to 208 mg/litre)	Tocilizumab 8 mg/kg (maximum 800 mg) intravenous infusion over 1 hour plus standard care. The dose could be repeated at 12 to 24 hours at the discretion of the clinician (29%; n=366).	Standard care including corticosteroids in most patients and remdesivir in about a third of patients (n=412).	**Primary outcome:** Respiratory and cardiovascular organ support-free days up to day 21. **Secondary outcomes:** In-hospital deaths. Median organ support-free days in survivors.

		in standard-care group.			
Hermine et al. 2021 (CORIMUNO-TOCI) Open-label randomised controlled trial 9 centres, France	n=131	Adults hospitalised with confirmed moderate or severe COVID-19 pneumonia (WHO-CPS score of 5) needing more than 3 litre/minute oxygen and not requiring intensive care admission. Without high-flow oxygen, non-invasive ventilation or mechanical ventilation. Median age (interquartile range: 64.0; 57.1 to 74.3) years. 68% male. Baseline median (IQR) CRP 120mg/litre (75 to 220 mg/litre) in tocilizumab group and 127 mg/litre (84 to 171 mg/litre) in standard-care group.	Tocilizumab 8 mg/kg intravenously on day 1 plus standard care. Additional dose of 400 mg intravenously on day 3 if oxygen requirement was not decreased by 50% (n=28, 47%). (n=63) Antivirals (n=7, 11%), corticosteroids (n=21, 33%), anticoagulants (n=59, 94%), additional immuno-modulator (n=1, 2% anakinra).	Standard care (including antibiotics, antivirals, corticosteroids, vasopressor support, and anticoagulants; n=67). Antivirals (n=16, 24%), corticosteroids (n=41, 61%), anticoagulants (n=61, 91%), additional immune-modulator (n=3, anakinra; n=1, eculizumab).	**Primary outcomes:** Scoring higher than 5 on the WHO-CPS on day 4 (death or mechanical ventilation). Non-invasive ventilation, mechanical ventilation or death. **Secondary outcomes:** Clinical status assessed with WHO-CPS scores. Mechanical ventilation or death. Admission to intensive care. Adverse events.
Horby et al. 2021 (RECOVERY, NCT04381936) Open-label randomised controlled trial 131 centres, UK	n=4,116	Adults hospitalised with suspected or confirmed severe COVID-19 with clinical evidence of progressive COVID-19 (defined as oxygen saturation less than 92% on room air or	Tocilizumab by body weight: • 800 mg if weight more than 90 kg • 600 mg if more than 65 kg to 90 kg or less • 400 mg if more than 40 kg to	Standard care Tocilizumab or sarilumab (n=44, 3%), corticosteroids (n=1721, 82%). (n=2,094)	**Primary outcome:** Mortality at 28 days **Secondary outcomes:** Time to discharge Mechanical ventilation or death

		receiving oxygen therapy, and CRP 75 mg/litre or more). Baseline respiratory support: • None (n=9) or supplemental oxygen only (45%). • Non-invasive ventilation including high-flow nasal cannula (41%). • Mechanical ventilation (14%). Mean (SD) age 63.6 (13.7) years. Median (IQR) CRP 143 mg/litre (107 to 204 mg/litre).	65 kg or less • 8 mg/kg if 40 kg or less intravenously plus standard care. Second dose given after 12 to 24 hours at discretion of clinician (n=461, 29%). ITT analysis, 83% of people allocated received at least 1 dose of tocilizumab. Corticosteroids (n=1664, 82%) (n=2,022)		Non-invasive respiratory support Time to successful cessation of mechanical ventilation Renal dialysis or haemofiltration
Salama et al. 2021 (EMPACTA) randomised controlled trial 6 countries (US, Mexico, Kenya, South Africa, Peru and Brazil)	n=389	Adults hospitalised with confirmed severe COVID-19 pneumonia with a blood oxygen saturation below 94% while breathing ambient air but not receiving non-invasive or mechanical ventilation at recruitment. Mean (SD) age 55.9 (14.4) years. Baseline respiratory support:	Tocilizumab 8 mg/kg intravenously up to a maximum of 800 mg (1 or 2 doses) plus standard care. Second dose given 8 to 24 hours after the first if status worsened or did not improve. (n=249) Antivirals (n=196, 78.7%), corticosteroids (n=200, 80.3%).	Placebo plus standard care (n=128). Antivirals (n=101 78.9%), corticosteroids (n=112, 87.5%).	**Primary outcome:** Mechanical ventilation or death by day 28. **Secondary outcomes:** Time to hospital discharge. Time to at least 2 category improvement in clinical status. Time to clinical failure or withdrawal. Mortality Progression of illness to category 6. Adverse events.

		• No supplemental oxygen (9.3%). • Supplemental oxygen (64.2%). • Non-invasive ventilation or high-flow oxygen (26.5%). 59.2% male. Tocilizumab group: 57.4% Hispanic or Latino, 14.1% black, and 13.3% American Indian or Alaska Native. Placebo group: 53.1% Hispanic or Latino, 16.4% black, and 11.7% American Indian or Alaska Native. Baseline median (range) CRP 136 mg/litre (3 to 3776 mg/litre).			
Salvarani et al. 2021 (RCT-TCZ-COVID-19) Open-label randomised controlled trial 24 hospitals, Italy	n=126	Adults hospitalised with confirmed severe COVID-19 pneumonia with acute respiratory failure with a PaO_2/FiO_2 ratio between 200 and 300 mm/Hg, and/or CRP greater than 10 mg/dl or increased to twice the admission level.	Tocilizumab 8 mg/kg intravenously up to a maximum of 800 mg, followed by a second dose after 12 hours. 5 adults had corticosteroids after clinical worsening. (n=60)	Standard care following the protocols of each clinical centre until clinical worsening and then could have tocilizumab as a rescue therapy (n=14). (n=63)	**Primary outcome:** Clinical worsening within 14 days. **Secondary outcomes:** Admission to intensive care. Deaths. Discharges.

		Baseline respiratory support: • Participants could have supplemental oxygen by mask or high-flow nasal cannula but could not have mechanical or non-invasive ventilation. Median (range) age 60.0 (53.0 to 72.0) years. 61.1% male. Baseline median (IQR) CRP 82 mg/litre (37 to 135 mg/litre).			
Stone et al. 2020 (BACC Bay Tocilizumab Trial) randomised controlled trial 7 centres, US	n=243	Adults hospitalised with confirmed severe COVID-19 pneumonia but not receiving mechanical ventilation. Baseline respiratory support: • No supplemental oxygen (16%). • Supplemental oxygen (80%). • Non-invasive ventilation or high-flow oxygen (4%). • Mechanical ventilation (less than 1%).	Tocilizumab 8 mg/kg intravenously as a single dose (maximum dose 800 mg) plus standard care, (n=161). Remdesivir (n=53, 33%), hydroxy-chloroquine (n=6, 4%), corticosteroids (n=18, 11%).	Placebo plus standard care (including remdesivir, hydroxy-chloroquine, and corticosteroids; n=81). Remdesivir (n=24, 29%), hydroxy-chloroquine (n=3, 4%), corticosteroids (n=5, 6%).	**Primary outcome:** Mechanical ventilation (or death if this occurred first) within 28 days. **Secondary outcomes:** Admission to intensive care or death. Clinical worsening. Stopping any supplemental oxygen. Adverse events.

		Median (range) age 59.8 (21.7 to 85.4) years. 58% male. 45% Hispanic or Latino, 16% black, and 43% white. Baseline median (IQR) CRP 110 mg/litre (65 to 175 mg/litre).			
Veiga et al. 2021 (TOCIBRAS) Open-label randomised controlled trial 9 centres Brazil	n=129	Adults with confirmed severe or critical COVID-19 who were receiving supplemental oxygen or mechanical ventilation (less than 24 hours) and had abnormal levels of at least 2 serum biomarkers (CRP, D-dimer, lactate dehydrogenase, or ferritin). Baseline respiratory support: • Supplemental oxygen (52%). • Non-invasive ventilation or high-flow oxygen (32%). • Mechanical ventilation (16%). Mean age (SD) 57 (14) years, 68% male.	Tocilizumab 8 mg/kg intravenously as a single dose plus standard care. Antibiotics (n=64, 95.5%), antivirals (n=7, 10.4%), corticosteroids (n=56, 83.6%). (n=65)	Standard care. Tocilizumab (n=2, 3.1%), antibiotics (n=61, 98.4%), antivirals (n=3, 4.8%), corticosteroids (n=55, 88.7%). (n=64)	**Primary outcome** Mechanical ventilation or death at 15 days Clinical status at 15 days **Secondary outcomes** All-cause mortality In-hospital mortality Sequential organ failure assessment score Clinical status Time to oxygen independence Duration of hospital stay Secondary infections Thromboembolic events Adverse events

		Baseline mean (SD) CRP 160mg/litre (104 mg/litre) in tocilizumab group and 193 mg/litre (283 mg/litre) in standard-care group.			

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; ITT, intention to treat; PaO_2/FiO_2, arterial oxygen partial pressure to fractional inspired oxygen ratio; SD, standard deviation; WHO-CPS, World Health Organization 10-point Clinical Progression Scale

Mechanical (invasive) ventilation: the patient is anesthetised, a tube inserted into the trachea, and attached to a mechanical ventilator.

Non-invasive ventilation: breathing support is given through a face mask, nasal mask or helmet.

In Gordon et al. (2021), patients were included who had suspected or proven SARS-CoV-2 infection with a severe disease state, defined by receiving respiratory or cardiovascular organ failure support in an intensive care unit. Respiratory organ support was defined as non-invasive or mechanical ventilation, including via high-flow nasal cannula if the flow rate was above 30 litres/minute and FiO_2 above 0.4. Pandemic surge capacity meant that provision of advanced organ support may have occurred in locations that do not usually provide intensive care. Therefore an intensive care unit was defined as an area of the hospital that has been repurposed to deliver organ support.

In Hermine et al. (2021) patients were included who had confirmed SARS-CoV-2 infection (positive on polymerase-chain-reaction test and/or typical chest computed tomographic scan) with moderate or severe pneumonia (O_2 greater than 3 litres/min, WHO Clinical Progression Scale [WHO-CPS] score equal to 5 [10-point ordinal scale]) but without high-flow oxygen, non-invasive ventilation or mechanical ventilation.

In Horby et al. (2021), patients were included who were hospitalised with suspected or confirmed severe COVID-19 with clinical evidence of progressive COVID-19

(defined as oxygen saturation less than 92% on room air or receiving oxygen therapy [hypoxia], and CRP 75 mg/litre or more [significant inflammation]).

In Salama et al. (2020) patients were included who were hospitalised with COVID-19 pneumonia confirmed by a positive polymerase-chain-reaction test and radiographic imaging. Patients had a blood oxygen saturation below 94% while breathing ambient air but were excluded if they were receiving continuous positive airway pressure, bilevel positive airway pressure or mechanical ventilation.

In Salvarani et al. (2021) patients were included who were hospitalised with COVID-19 pneumonia confirmed by a positive polymerase-chain-reaction test. Patients had acute respiratory failure with a PaO_2/FIO_2 ratio between 200 and 300 mm/Hg, an inflammatory phenotype defined by a temperature greater than 38°C during the previous 2 days, and/or serum C-reactive protein (CRP) levels of 10 mg/dl or more and/or CRP level increased to at least twice the admission measurement. Patients at enrolment were allowed to receive oxygen therapy with a mask or high-flow nasal cannula, but not mechanical or non-invasive ventilation. Patients were excluded if they were admitted to intensive care.

In Stone et al. (2020) patients were included if they had SARS-CoV-2 infection confirmed by either nasopharyngeal swab polymerase chain reaction or serum IgM antibody assay. Patients had at least 2 of the following signs: fever (body temperature above 38°C) within 72 hours before enrolment, pulmonary infiltrates or a need for supplemental oxygen to maintain an oxygen saturation higher than 92%. At least 1 of the following laboratory criteria also had to be fulfilled: a CRP level higher than 50 mg/litre, a ferritin level higher than 500 ng/ml, and-dimer level higher than 1000 ng/ml or a lactate dehydrogenase level higher than 250 U/litre. Patients were excluded if they were receiving supplemental oxygen at more than 10 litre/minute.

In Veiga et al. (2021), patients were included if they had confirmed SARS-CoV-2 infection, computed tomography or a chest X-ray consistent with COVID-19, more than 3 days of symptoms related to COVID-19, a need for oxygen supplementation to maintain oxygen saturation greater than 93% or were receiving mechanical ventilation for less than 24 hours before randomisation. Patients also had to have 2 or more of the following: a D-dimer level greater than 1,000 ng/ml, a CRP level

greater than 5 mg/dl, a ferritin level greater than 300 mg/dl or a lactate dehydrogenase level greater than the upper limit of normal.

Appendix C: Quality assessment of included studies

Quality assessment of Gordon et al. (2021; based on prepublication manuscript)

Overall risk of bias assessed by Cochrane authors as 'some concerns' because of deviations from intervention and measurement of the outcome using Cochrane risk of bias 2 tool. See the description of primary studies in the COVID-NMA initiative for full details.

Quality assessment of Hermine et al. (2021)

Overall risk of bias assessed by Cochrane authors as 'some concerns' because of deviations from intervention and measurement of the outcome using Cochrane risk of bias 2 tool. See the description of primary studies in the COVID-NMA initiative for full details.

Quality assessment of Horby et al. (2021; based on prepublication manuscript)

Question	Horby et al. 2021
Domain 1	Risk of bias arising from the randomisation process
1.1 Was the allocation sequence random?	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Risk of bias judgement	Low
Domain 2	Risk of bias because of deviations from the intended interventions (effect of assignment to intervention)
2.1. Were participants aware of their assigned intervention during the trial?	Yes
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Probably no
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Not applicable

2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Not applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Risk of bias judgement	Low
Domain 3	Missing outcome data
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	Low
Domain 4	Risk of bias in measurement of the outcome
4.1 Was the method of measuring the outcome inappropriate?	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably yes
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Yes
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No information
Risk of bias judgement	Some concerns
Domain 5	Risk of bias in selection of the reported result
5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis?	Yes
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome	No

measurements (for example, scales, definitions, time points) within the outcome domain?	
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No
Risk of bias judgement	Low
Overall risk of bias judgement	Some concerns

Checklist used: Cochrane risk of bias 2 tool.

Abbreviations: Y, Yes; PY, Probably yes; PN, Probably no; N, No; NI, No information.

Quality assessment of Salama et al. (2021)

Overall risk of bias assessed by Cochrane authors as 'low' using the Cochrane risk of bias 2 tool. See the description of primary studies in the COVID-NMA initiative for full details.

Quality assessment of Salvarani et al. (2021)

Overall risk of bias assessed by Cochrane authors as 'some concerns' because of deviations from intervention and measurement of the outcome using the Cochrane risk of bias 2 tool. See the description of primary studies in the COVID-NMA initiative for full details.

Quality assessment of Stone et al. (2020)

Overall risk of bias assessed by Cochrane authors as 'low' using the Cochrane risk of bias 2 tool. See the description of primary studies in the COVID-NMA initiative for full details.

Quality assessment of Veiga et al. (2021)

Overall risk of bias assessed by Cochrane authors as 'some concerns' because of deviations from intervention and measurement of the outcome using Cochrane risk of bias 2 tool. See the description of primary studies in the COVID-NMA initiative for full details.

Appendix D: Results tables

Results table for Gordon et al. 2021

Outcome	Tocilizumab	Standard care	Analysis
Primary outcome	**n=353**	**n=402**	**-**
Median organ support-free days 21 days	10 (IQR -1 to 16)	0 (IQR -1 to 15)	Median aOR 1.64 (95% CrI 1.25 to 2.14, more than 99.9% posterior probability of superiority)
Hospital survival (survival during hospital admission)	-	-	Median aOR 1.64 (95% CrI 1.14 to 2.35, 99.6% posterior probability of superiority)
Secondary outcomes	**n=353**	**n=402**	**-**
In-hospital deaths (subcomponent of 'organ support-free days') Timescale not reported	98/350 (28.0%)	142/397 (35.8%)	-
Median organ support-free days in survivors (subcomponent of 'organ support-free days') 21 days	14 (IQR 7 to 17)	13 (IQR 4 to 17)	-
Survival (time to event) 90 days	-	-	Median aHR 1.59 (95% CrI 1.24 to 2.05, more than 99.9% posterior probability of superiority)
Time to hospital discharge 90 days	-	-	Median aHR 1.41 (95% CrI 1.18 to 1.70, more than 99.9% posterior probability of superiority)
Time to discharge from intensive care 90 days	-	-	Median aHR 1.42 (95% CrI 1.18 to 1.70, more than 99.9% posterior

			probability of superiority)
WHO scale 14 days	-	-	Median aOR 1.83 (95% CrI 1.40 to 2.41, more than 99.9% posterior probability of superiority)
Invasive mechanical ventilation, extracorporeal membrane oxygenation or death (in those not intubated at baseline)	100/242 (41.3%)	144/273 (52.7%)	Median aOR 1.69 (95% CrI 1.17 to 2.42, 99.8% posterior probability of superiority)
Safety outcomes	**n=353**	**n=402**	**-**
Serious adverse events	9/353 (2.5%)	11/402 (2.7%)	Median aOR 1.10 (95% CrI 0.48 to 2.58, probability of superiority 59.3%)

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CrI, credible interval; IQR, interquartile range; WHO scale, World Health Organization scale ranging from 0 (no disease) to 8 (death).

Median organ support-free days includes days free of respiratory and cardiovascular organ support and death, where all deaths were assigned a value of -1.

Results table for Hermine et al. 2021

Outcome	Tocilizumab plus standard care	Standard care	Analysis
Primary outcomes	**n=63**	**n=67**	**-**
Non-invasive ventilation, mechanical ventilation or death (WHO-CPS more than 5) 4 days	12/63 (19%)	19/67 (28%)	Median posterior ARD -9.0%, (90% CrI -21.0% to 3.1%)
Non-invasive ventilation, mechanical ventilation or death 14 days	15/63 (24%)	24/67 (36%)	ARD -12% (95% CI -28% to 4%) Median posterior HR 0.58 (90% CrI, 0.33 to 1.00)
Secondary outcomes	**n=63**	**n=67**	**-**
Clinical status (WHO-CPS)	5 (IQR 5 to 5)	5 (IQR 5 to 6)	aOR 0.86 (95% CrI 0.43 to 1.71)

Outcome	Tocilizumab plus standard care	Standard care	Analysis
7 days			
Clinical status (WHO-CPS) 14 days	2 (IQR 2 to 5)	4 (IQR 2 to 7)	aOR 0.76 (95% CrI 0.40 to 1.42)
Mechanical ventilation or death 28 days	7/63	8/67	HR 0.58 (90% CrI, 0.30 to 1.09) aHR 0.92 (95% CI, 0.33 to 2.53)
Admission to intensive care (in people who were not in intensive care at randomisation) 14 days	11/60 (18%)	22/64 (36%)	RD -18% (95% CI, 0.4% to -31%) Post-hoc analysis
Safety outcomes	**n=63**	**n=67**	**-**
Adverse events 28 days	28/63 (44%)	36/67 (54%)	p=0.30
Serious adverse events 28 days	20/63 (32%)	29/67 (43%)	p=0.21

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; ARD, absolute risk difference; CI, confidence interval; CrI, credible interval; HR, hazard ratio; IQR, interquartile range; RD, risk difference; WHO-CPS, World Health Organization 10-point Clinical Progression Scale

The primary outcomes were the proportion of people dead or receiving non-invasive or mechanical ventilation at day 4 (greater than 5 on the WHO-CPS scale) and survival with no need for non-invasive or mechanical ventilation at day 14. The outcomes were amended on 6 April 2020 to include high-flow oxygen in non-invasive ventilation to be consistent with the WHO-CPS definition.

Results table for Horby et al. 2021

Outcome	Tocilizumab	Standard care	Analysis
Primary outcome	**n=2022**	**n=2094**	**-**
Death 28 days	596/2022 (29%)	694/2094 (33%)	RR 0.86 (95% CI 0.77 to 0.96, p=0.0066)
Secondary outcomes	**n=2022**	**n=2094**	**-**
Median time to discharge (days)	20	more than 28	-

Discharge 28 days	1093/2022 (54%)	990/2094 (47%)	RR 1.23 (95% CI 1.12 to 1.34, p<0.0001)
Mechanical ventilation or death (in people not on mechanical ventilation at baseline) 28 days	571/1754 (33%)	687/1800 (38%)	Risk ratio 0.85 (95% CI 0.78 to 0.93, p=0.0005)
Ventilation (non-invasive or mechanical, in people not on ventilation at baseline) 28 days	233/935 (25%)	242/933 (26%)	Risk ratio 0.96 (95% CI 0.82 to 1.12, p=0.61)
Non-invasive ventilation (in people not on ventilation at baseline) 28 days	222/935 (24%)	223/933 (24%)	Risk ratio 0.99 (95% CI 0.84 to 1.17, p=0.94)
Mechanical ventilation (in people not on ventilation at baseline) 28 days	45/935 (5%)	63/933 (7%)	Risk ratio 0.71 (95% CI 0.49 to 1.03, p=0.07)
Successful cessation of mechanical ventilation (in people on mechanical ventilation at baseline) 28 days	91/268 (34%)	94/294 (32%)	RR 1.07 (95% CI 0.80 to 1.43, p=0.64)
Haemodialysis or haemofiltration 28 days	103/2003 (5%)	142/2075 (7%)	Risk ratio 0.75 (95% CI 0.59 to 0.96, p=0.02)
Subgroup analyses	**n=2022**	**n=2094**	-
Age, years less than 70	256/1332 (19%)	289/1354 (21%)	RR 0.88 (95% CI 0.74 to 1.04)
Age, years 70 or more and less than 80	206/477 (43%)	234/480 (49%)	RR 0.84 (95% CI 0.69 to 1.01)
Age, years 80 or more	134/213 (63%)	171/260 (66%)	RR 0.93 (95% CI 0.74 to 1.17)
Men	400/1335 (30%)	504/1437 (35%)	RR 0.81 (95% CI 0.71 to 0.93)
Women	196/687 (29%)	190/657 (29%)	RR 0.98 (95% CI 0.80 to 1.20)
Ethnicity, white	429/1356 (32%)	519/1426 (36%)	RR 0.83 (95% CI 0.73 to 0.95)
Ethnicity, black, Asian, or minority ethnic	98/341 (29%)	110/357 (31%)	RR 0.91 (95% CI 0.69 to 1.20)
Days since symptom onset 7 or less or less	210/668 (31%)	245/660 (37%)	RR 0.81 (95% CI 0.67 to 0.97)
Days since symptom onset more than 7	386/1354 (29%)	449/1433 (31%)	RR 0.88 (95% CI 0.77 to 1.01)

No ventilator support at baseline	175/935 (19%)	202/933 (22%)	RR 0.84 (95% CI 0.69 to 1.03)
Non-invasive ventilator support at baseline	296/819 (36%)	350/867 (40%)	RR 0.86 (95% CI 0.74 to 1.01)
Mechanical ventilation at baseline	125/268 (47%)	142/294 (48%)	RR 0.94 (95% CI 0.73 to 1.19)
Corticosteroid use	457/1664 (27%)	565/1721 (33%)	RR 0.80 (95% CI 0.70 to 0.90)
No corticosteroid use	139/357 (39%)	127/367 (35%)	RR 1.16 (95% CI 0.91 to 1.48)
Safety outcomes	**n=2022**	**n=2094**	**-**
Serious adverse reactions	3 serious adverse reactions believed to be related to tocilizumab: otitis externa, *Staphylococcus aureus* bacteraemia, and lung abscess. All resolved with standard treatment.	-	No statistical analysis reported.

Abbreviations: CI, confidence interval; RR, rate ratio

Results table for Salama et al. 2021

Outcome	Tocilizumab	Placebo	Analysis
Primary outcome	**n=249**	**n=128**	**-**
Mechanical ventilation or death 28 days	12.0% (95% CI 8.5 to 16.9%)	19.3% (95% CI 13.3 to 27.4%)	HR 0.56 (95% CI 0.33 to 0.97, p=0.04)
Secondary outcomes	**n=249**	**n=128**	**-**
Median time to hospital discharge or readiness for discharge (days) 28 days	6.0 (95% CI 6.0 to 7.0)	7.5 (95% CI 7.0 to 9.0)	HR 1.16 (95% CI 0.91 to 1.48)
Median time to improvement in clinical status (days) 28 days	6.0 (95% CI 6.0 to 7.0)	7.0 (95% CI 6.0 to 9.0)	HR 1.15 (95% CI 0.90 to 1.48)
Median time to clinical failure or withdrawal 28 days	Could not be estimated	Could not be estimated	HR 0.55 (95% CI 0.33 to 0.93)
Deaths 28 days	10.4% (95% CI 7.2 to 14.9%)	8.6% (95% CI 4.9 to 14.7%)	Weighted difference 2.0% (95% CI -5.2 to 7.8%)
Progression of illness to category 6	8/250 (3.2%)	6/127 (4.7%)	-

Outcome	Tocilizumab	Placebo	Analysis
28 days			
Safety outcomes	**n=249**	**n=12**	**-**
Serious adverse events by day 60	15.2%	19.7%	-
Death by day 60	29 (11.6%)	15 (11.8%)	-
Serious infections	13 (5.2%)	9 (7.1%)	-

Abbreviations: CI, confidence interval; HR, hazard ratio

Improvement in clinical status and progression of illness was assessed using the 7-category ordinal scale with categories ranging from 1 to 7, where higher categories indicate a worse condition. 'Category 1 indicated that the patient was discharged (or ready for discharge as evidenced by normal body temperature and respiratory rate, as well as stable oxygen saturation while breathing ambient air or 2 litres or less of supplemental oxygen); 2, hospitalised in a non-intensive care unit (ICU) hospital ward (or ready for a hospital ward) and not receiving supplemental oxygen; 3, hospitalised in a non-ICU hospital ward (or ready for a hospital ward) and receiving supplemental oxygen; 4, hospitalised in an ICU or a non-ICU hospital ward and receiving non-invasive ventilation or high-flow oxygen; 5, hospitalised in an ICU and receiving intubation and mechanical ventilation; 6, hospitalised in an ICU and receiving extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; and 7, died.'

Clinical failure was defined as either death, mechanical ventilation or admission to intensive care.

Results table for Salvarani et al. 2021

Outcome	Tocilizumab	Standard care	Analysis
Primary outcome	**n=60**	**n=63**	**-**
Clinical worsening 14 days	17/60 (28.3%)	17/63 (27.0%)	RR 1.05 (95% CI 0.59 to 1.86, p=0.87)
Secondary outcomes	**n=60**	**n=63**	**-**
Admission to intensive care 14 days	6/60 (10.0%)	5/ 63 (7.9%)	RR 1.26 (95% CI 0.41 to 3.91)
Admission to intensive care 30 days	6/60 (10.0%)	5/63 (7.9%)	RR 1.26 (95% CI 0.41 to 3.91)

Outcome	Tocilizumab	Standard care	Analysis
Deaths 14 days	1/60 (1.7%)	1/63 (1.6%)	RR 1.05 (95% CI 0.07 to 16.4)
Deaths 30 days	2/60 (3.3%)	1/63 (1.6%)	RR 2.10 (95% CI 0.20 to 22.6)
Discharges 14 days	34/60 (56.7%)	36/63 (57.1%)	RR 0.99 (95% CI 0.73 to 1.35)
Discharges 30 days	54/60 (90.0%)	58/63 (92.1%)	RR 0.98 (95% CI 0.87 to 1.09)
Safety outcomes	**n=60**	**n=63**	**-**
Adverse events	14/60 (23.3%)	7/63 (11.1%)	-
Laboratory abnormalities	8/60 (13.3%) Increased alanine aminotransferase (n=5) Decreased neutrophil count (n=3)	2/63 (3.2%) Increased alanine aminotransferase (n=2)	-

Abbreviations: CI, confidence interval; RR, rate ratio

Clinical worsening was defined as occurrence of 1 of the following: admission to intensive care with mechanical ventilation, death or an arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FIO_2) ratio less than 150 mm Hg.

Results table for Stone et al. 2020

Outcome	Tocilizumab	Placebo	Analysis
Primary outcome	**n=161**	**n=81**	**-**
Mechanical ventilation or death 28 days	17/161 (10.6% [95% CI 6.7 to 16.6%])	10/81 (12.5% [95% CI 6.9 to 22.0%])	HR 0.83 (95% CI 0.38 to 1.81, p=0.64) aHR 0.66 (95% CI 0.28 to 1.52)
Secondary outcomes	**n=161**	**n=81**	**-**
Admission to intensive care or death 28 days	15.9%	15.8%	RR 0.97 (95% CI 0.50 to 1.88)
Median duration of mechanical ventilation (days) 28 days	15.0 (IQR 12.6 to NR)	27.9 (IQR 16.3 to NR)	-
Time to clinical worsening 28 days	31/161 (19.3%)	14/81 (17.4%)	HR 1.11 (95% CI 0.59 to 2.10, p=0.73) aHR 0.88 (95% CI 0.45 to 1.72)

Outcome	Tocilizumab	Placebo	Analysis
Clinical worsening (WHO-CPS) 14 days	18%	14.9%	-
Time to stopping supplemental oxygen (median) 28 days	5.0 (IQR 3.8 to 7.8)	4.9 (IQR 3.8 to 7.8)	HR 0.94 (95% CI 0.67 to 1.30, p=0.69) aHR 0.95 (95% CI 0.67 to 1.33)
Safety outcomes	**n=161**	**n=82**	**-**
Serious adverse events	28/161	12/82	-
Neutropenia	22/161 (13.7%)	1/82 (1.2%)	p=0.002
Serious infections	13/161 (8.1%)	14/82 (17.1%)	p=0.03

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; IQR, interquartile range; RR, risk ratio

Clinical worsening was defined as an increase in score on the ordinal clinical improvement scale by at least 1 point among patients receiving supplemental oxygen at baseline or at least 2 points among those not receiving supplemental oxygen at baseline. Improvement was defined as an increase in score by at least 2 points.

Results table for Veiga et al. 2021

Outcome	Tocilizumab	Standard care	Analysis
Primary outcome	**n=65**	**n=64=**	**-**
Mechanical ventilation or death 15 days	18/65 (28%)	13/64 (20%)	OR 1.54 (95% CI 0.66 to 3.66, p=0.32)
Death 15 days	11/65 (17%)	2/64 (3%)	OR 6.42 (95% CI 1.59 to 43.2)
Secondary outcomes	**n=65**	**n=64**	**-**
Death 28 days	14/65 (21%)	6/64 (9%)	2.70 (95% CI, 0.97 to 8.35, p=0.07)
In-hospital mortality	14/65 (21%)	6/64 (9%)	2.70 (95% CI 0.97 to 8.35, p=0.02)
Mean (SD) SOFA score 8 days	4.1 (3.9)	3.4 (3.0)	Mean ratio 1.20 (95% CI 0.87 to 1.64, p=0.26)
Mean (SD) SOFA score 15 days	4.3 (3.6)	4.3 (3.6)	Mean ratio 0.99 (95% CI 0.65 to 1.49, p=0.95)

Outcome	Tocilizumab	Standard care	Analysis
Clinical status (6 level ordinal scale, 1 to 4 compared with 5 to 6)) 8 days	1 to 4: 41/65 (63.1%) 5 to 6: 24/65 (36.9%)	1 to 4: 39/64 (60.9%) 5 to 6: 25/64 (39.1%)	OR 0.91 (95% CI 0.44 to 1.89, p=0.79)
Clinical status (7 level ordinal scale, 1 to 5 compared with 6 to 7) 29 days)	1 to 5: 47/65 (72.3%) 6 to 7: 18/65 (27.7%)	1 to 5: 54/64 (84.4%) 6 to 7: 10/64 (15.6%)	OR 2.17 (95% CI 0.88 to 5.60, p=0.10)
Mean (SD) ventilator-free days 29 days	19.4 (12.0)	20.5 (10.8)	RR 1.12 (95% CI 0.86 to 1.99, p=0.53)
Median (IQR) time to supplemental oxygen independence 29 days	6 (5 to 12)	10 (8 to 14)	HR 1.37 (95% CI 0.92 to 2.04, p=0.12)
Mean (SD) duration of hospital stay (days)	11.3 (8.0)	14.7 (8.2)	RR 0.70 (95% CI 0.55 to 0.87, p=0.001)
Safety outcomes	**n=67**	**n=62**	**-**
Adverse events	29/67 (43%)	21/62 (34%)	p=0.26
Severe adverse events	11/67 (16%)	7/62 (11%)	p=0.45
Secondary infections	10/65 (15%)	10/64 (16%)	OR 0.99 (95% 0.37 to 2.67, p=0.98)
Thromboembolic events	3/65 (5%)	4/64 (6%)	OR 0.72 (95% CI 0.14 to 3.40, p=0.67)

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; OR, odds ratio; RR, rate ratio; SD, standard deviation; SOFA, sequential organ failure assessment

Clinical status was measured at 8 days on a 6-level ordinal scale: 1, not admitted to hospital; 2, admitted to hospital not receiving supplemental oxygen; 3, admitted to hospital receiving supplemental oxygen; 4, admitted to hospital receiving non-invasive ventilation or high-flow oxygen through a nasal cannula; 5, admitted to hospital receiving mechanical ventilation; 6, death.

Clinical status was measured at 29 days on a 7-level ordinal scale: 1, not admitted to hospital no limitation on activities; 2, not admitted to hospital limitation on activities; 3, admitted to hospital not receiving supplemental oxygen; 4, admitted to hospital receiving supplemental oxygen; 5, admitted to hospital receiving non-invasive

ventilation or high-flow oxygen through a nasal cannula; 6, admitted to hospital receiving mechanical ventilation; 7, death.

Appendix E: Literature search strategy

Database	Platform	Segment searched
MEDLINE ALL	Ovid	1946 to December 31, 2020. Update to February 09, 2021.
Embase	Ovid	1974 to 2020 December 31. Update to February 09, 2021.
Cochrane Library	Wiley	Issue 1 of 12, 2021 (same for Cochrane Database of Systematic Reviews and CENTRAL databases). Update issue 2 of 12 February 2021.
WHO COVID-19 database	WHO website	-

Source	No. of results (31 December 2020)	No. of results (09 February 2021)
MEDLINE ALL	266	173
Embase	514	81
Cochrane Library - CDSR	0	0
Cochrane Library - Central	33	15
WHO COVID-19 database	309	28
Unpublished manuscript	1	1
Total results	1123	297
Total after deduplications	812	269

Database strategies

MEDLINE ALL

1 (tocilizumab* or toclizumab*).af. (4114)
2 (actemra or RoActemra).af. (71)
3 atlizumab.af. (19)
4 lusinex.af. (1)
5 (R-1569 or R1569).af. (7)
6 or/1-5 (4141)
7 exp coronavirus/ (45349)
8 exp Coronavirus Infections/ (49593)
9 COVID-19/ (7818)
10 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (2605)
11 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw,kf. (60205)
12 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw,kf. (84474)

13 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (310)
14 (("seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (97)
15 (pneumonia* adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (554)
16 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (348)
17 "severe acute respiratory syndrome*".ti,ab,kw,kf. (15357)
18 or/7-17 (110526)
19 limit 18 to yr="2019 -Current" (91111)
20 6 and 19 (762)
21 randomized controlled trial.pt. (519902)
22 random*.mp. (1425570)
23 placebo.mp. (221234)
24 controlled clinical trial/ (93994)
25 clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ (52249)
26 equivalence trial/ (695)
27 pragmatic clinical trial/ (1595)
28 trial.tw. (624174)
29 trials.tw. (579810)
30 intervention.tw. (627243)
31 interventions.tw. (480733)
32 or/21-31 (2808623)
33 20 and 32 (254)
34 (MEDLINE or pubmed).tw. (224236)
35 systematic review.tw. (173746)
36 systematic review.pt. (142124)
37 meta-analysis.pt. (124367)
38 intervention$.ti. (157064)
39 or/34-38 (494913)
40 20 and 39 (52)
41 33 or 40 (266)

Embase

1 tocilizumab/ (14204)
2 (tocilizumab* or toclizumab*).af. (14799)
3 (actemra or RoActemra).af. (764)
4 atlizumab.af. (566)
5 lusinex.af. (1)
6 (R-1569 or R1569).af. (12)
7 or/1-6 (15196)
8 exp Coronavirinae/ (22679)
9 exp Coronavirus infection/ (24291)
10 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").sh,dj. (77629)
11 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (2048)
12 (coronavirus* or coronovirus* or coronavirinae* or CoV).ti,ab,kw. (60494)
13 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or

"SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw. (81580)
14 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (384)
15 (("seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (101)
16 (pneumonia* adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (614)
17 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (159)
18 "severe acute respiratory syndrome*".ti,ab,kw. (15280)
19 or/8-18 (115569)
20 limit 19 to yr="2019 -Current" (92154)
21 limit 20 to medline (22082)
22 20 not 21 (70072)
23 7 and 22 (1872)
24 random:.tw. (1619638)
25 placebo:.mp. (467592)
26 double-blind:.tw. (216694)
27 exp randomized controlled trial/ (640142)
28 trial.tw. (901418)
29 trials.tw. (804435)
30 intervention.tw. (932798)
31 interventions.tw. (598941)
32 or/24-31 (3748808)
33 23 and 32 (449)
34 (MEDLINE or pubmed).tw. (282299)
35 exp systematic review/ or systematic review.tw. (331919)
36 meta-analysis/ (204973)
37 intervention$.ti. (210691)
38 or/34-37 (705559)
39 23 and 38 (131)
40 33 or 39 (514)

Cochrane Library (CDSR and CENTRAL)

#1 [mh "COVID-19"]
#2 MeSH descriptor: [Coronavirus] explode all trees
#3 MeSH descriptor: [Coronavirus Infections] explode all trees
#4 ((corona* or corono*) near/1 (virus* or viral* or virinae*)):ti,ab,kw
#5 (coronavirus* or coronovirus* or coronavirinae* or CoV):ti,ab,kw
#6 ("2019 nCoV" or 2019nCoV* or "19 nCoV" or 19nCoV* or nCoV2019* or "nCoV 2019" or nCoV19* or "nCoV 19" or "COVID 19" or COVID19* or "COVID 2019" or COVID2019* or "HCoV 19" or HCoV19* or "HCoV 2019" or HCoV2019* or "2019 novel" or Ncov* or "n cov" or "SARS CoV 2" or "SARSCoV 2" or "SARSCoV2" or "SARS CoV2" or SARSCov19* or "SARS Cov19" or "SARSCov 19" or "SARS Cov 19" or SARSCov2019* or "SARS Cov2019" or "SARSCov 2019" or "SARS Cov 2019" or SARS2* or "SARS 2" or SARScoronavirus2* or "SARS coronavirus 2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2* or "SARS coronovirus 2" or "SARScoronovirus 2" or "SARS coronovirus2" or covid):ti,ab,kw
#7 (respiratory* near/2 (symptom* or disease* or illness* or condition*) near/5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw
#8 (("seafood market" or "seafood markets" or "food market" or "food markets") near/10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw

#9 (pneumonia* near/3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw
#10 ((outbreak* or wildlife* or pandemic* or epidemic*) near/1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw
#11 ("severe acute respiratory syndrome" or "severe acute respiratory syndromes"):ti,ab,kw
#12 {or #1-#11}
#13 (tocilizumab* or toclizumab*):ti,ab,kw
#14 (actemra or RoActemra):ti,ab,kw
#15 atlizumab:ti,ab,kw
#16 lusinex:ti,ab,kw
#17 "R-1569":ti,ab,kw
#18 R1569:ti,ab,kw
#19 {or #13-#18}
#20 #12 AND #19
#21 (trialsearch OR clinicaltrials):so
#22 #20 NOT #21

Appendix F: Excluded studies

Study reference	Reason for exclusion
Abrams-Downey, Alexandra; Saabiye, Joseph; Vidaurrazaga, Monica (2020) Investigational Therapies for the Treatment of COVID-19: Updates from Ongoing Clinical Trials. European urology focus 6(5): 1028-1031	Study design – narrative review
Algazaq, J.; Hiraldo-Infante, C.; Miskovsky, J. (2020) Tocilizumab treatment in COVID-19-induced cytokine release syndrome. Infectious Diseases in Clinical Practice 28(6): e76-e78	Study design – letter
Alzghari, Saeed K and Acuna, Valerie S (2020) Supportive Treatment with Tocilizumab for COVID-19: A Systematic Review. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology 127: 104380	Study design - systematic review included observational studies
Aziz, Muhammad, Haghbin, Hossein, Abu Sitta, Emad et al. (2020) Efficacy of tocilizumab in COVID-19: A systematic review and meta-analysis. Journal of medical virology	Study design - systematic review included observational studies
Bendezu-Quispe, Guido, Rodriguez-Zuniga, Milton Jose Max, Roman, Yuani Miriam et al. (2020) No title provided. Revista peruana de medicina experimental y salud publica 37(2): 320-326	Study design – narrative review
Berardicurti, Onorina, Ruscitti, Piero, Ursini, Francesco et al. (2020) Mortality in tocilizumab-treated patients with COVID-19: a systematic review and meta-analysis. Clinical and experimental rheumatology 38(6): 1247-1254	Study design - systematic review included observational studies
Boregowda, Umesha, Perisetti, Abhilash, Nanjappa, Arpitha et al. (2020) Addition of Tocilizumab to the Standard of Care Reduces Mortality in Severe COVID-19: A Systematic	Study design - systematic review included observational studies

Review and Meta-Analysis. Frontiers in medicine 7: 586221	
Campbell, C.M., Guha, A., Haque, T. et al. (2020) Repurposing immunomodulatory therapies against coronavirus disease 2019 (Covid-19) in the era of cardiac vigilance: a systematic review. Journal of Clinical Medicine 9(9): 1-24	Study design - systematic review included observational studies
Cantini, Fabrizio, Goletti, Delia, Petrone, Linda et al. (2020) Immune Therapy, or Antiviral Therapy, or Both for COVID-19: A Systematic Review. Drugs 80(18): 1929-1946	Study design - systematic review included observational studies
Di Lorenzo, Giuseppe, Di Trolio, Rossella, Kozlakidis, Zisis et al. (2020) COVID 19 therapies and anti-cancer drugs: A systematic review of recent literature. Critical reviews in oncology/hematology 152: 102991	Study design – narrative review
Falavigna, Maicon, Colpani, Veronica, Stein, Cinara et al. (2020) Guidelines for the pharmacological treatment of COVID-19. The task-force/consensus guideline of the Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology. Revista Brasileira de terapia intensiva 32(2): 166-196	Study design - systematic review included observational studies
Gokhale, Y., Mehta, R., Karnik, N. et al. (2020) Tocilizumab improves survival in patients with persistent hypoxia in severe COVID-19 pneumonia. EClinicalMedicine 24: 100467-100467	Study design – letter
Gudadappanavar, Anupama M and Benni, Jyoti (2020) An evidence-based systematic review on emerging therapeutic and preventive strategies to treat novel coronavirus (SARS-CoV-2) during an outbreak scenario. Journal of basic and clinical physiology and pharmacology 31(6)	Study design – narrative review
Khalili, M., Chegeni, M., Javadi, S. et al. (2020) Therapeutic interventions for COVID-19: a living overview of reviews. Therapeutic Advances in Respiratory Disease 14	Study design – systematic review included observational studies
Khan, S., Gionfriddo, M.R., Cortes-Penfield, N. et al. (2020) The trade-off dilemma in pharmacotherapy of COVID-19: systematic review, meta-analysis, and implications. Expert Opinion on Pharmacotherapy 21(15): 1821-1849	Study design – review of multiple interventions
Kim, Min Seo, An, Min Ho, Kim, Won Jun et al. (2020) Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. PLoS medicine 17(12): e1003501	Study design - systematic review included observational studies
Liberato, Nicola Lucia, De Monte, Andrea, Caravella, Giuseppe (2020) Tocilizumab in severe	Study design – letter

COVID-19. Archives of Medical Science 16(6): 1457-1458	
Mansourabadi, A.H., Sadeghalvad, M., Mohammadi-Motlagh, H.-R. et al. (2020) The immune system as a target for therapy of SARS-CoV-2: A systematic review of the current immunotherapies for COVID-19. Life Sciences 258: 118185	Study design - systematic review included observational studies
Misra, Shubham, Nath, Manabesh, Hadda, Vijay et al. (2020) Efficacy of various treatment modalities for nCOV-2019: A systematic review and meta-analysis. European journal of clinical investigation 50(11): e13383	Study design - systematic review included observational studies and in vitro
Najar Nobari, Niloufar, Seirafianpour, Farnoosh, Mashayekhi, Farzaneh et al. (2020) A systematic review on treatment-related mucocutaneous reactions in COVID-19 patients. Dermatologic therapy: e14662	Study design - systematic review included observational studies
Potere, N., Nisio, M. di, Rizzo, G., Vella, M. la, Polilli, E. et al. (2020) Low-dose subcutaneous tocilizumab to prevent disease progression in patients with moderate COVID-19 pneumonia and hyperinflammation. (Special Issue: Coronavirus (COVID-19) collection.). International Journal of Infectious Diseases 100: 421-424	Study design – observational study
Russell, B., Moss, C., George, G. et al. (2020) Associations between immune-suppressive and stimulating drugs and novel COVID-19 - A systematic review of current evidence. ecancermedicalscience 14: e1022	Study design - systematic review included observational studies
Sarfraz, Azza, Sarfraz, Zouina, Sarfraz, Muzna et al. (2020) Tocilizumab and COVID-19: A Meta-Analysis of 2120 Patients with Severe Disease and Implications for Clinical Trial Methodologies. Turkish journal of medical sciences	Study design - systematic review included prepublication studies
Schoot, Tessa S, Kerckhoffs, Angele P M, Hilbrands, Luuk B et al. (2020) Immunosuppressive Drugs and COVID-19: A Review. Frontiers in pharmacology 11: 1333	Study design - systematic review included observational studies
Shah, Nirali N., Ivy, Percy, Enos, Rebecca et al. (2020) Expanded access trial of tocilizumab in COVID19+hospitalized cancer patients. Clinical Cancer Research 26(18)	Study design – non-comparative
Siordia, Juan A Jr, Bernaba, Michael, Yoshino, Kenji et al. (2020) Systematic and Statistical Review of Coronavirus Disease 19 Treatment Trials. SN comprehensive clinical medicine: 1-12	Study design - systematic review included observational studies
Solis-Garcia Del Pozo, J, Galindo, M F, Nava, E et al. (2020) A systematic review on the efficacy and safety of IL-6 modulatory drugs in the treatment of COVID-19 patients. European review for medical and pharmacological sciences 24(13): 7475-7484	Study design - systematic review included observational studies

Talaie, Haleh, Hosseini, Sayed Masoud, Nazari, Maryam et al. (2020) Is there any potential management against COVID-19? A systematic review and meta-analysis. Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences 28(2): 765-777	Study design – review of multiple interventions
Tleyjeh, Imad M, Kashour, Zakariya, Damlaj, Moussab et al. (2020) Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases	Study design - systematic review included observational studies
Xu, X., Han, M., Li, T. et al. (2020) Tocilizumab treatment in COVID-19 patients needs the assessment of the disease severity and timely intervention. Proceedings of the National Academy of Sciences of the United States of America 117(48): 30027-30028	Study design – letter
Zhao, Hong, Zhu, Qi, Zhang, Chi et al. (2021) Tocilizumab combined with favipiravir in the treatment of COVID-19: A multicenter trial in a small sample size. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 133: 110825	Comparator is not placebo or standard care
Zhao, Jie; Cui, Wei; Tian, Bao-Ping (2020) Efficacy of tocilizumab treatment in severely ill COVID-19 patients. Critical care (London, England) 24(1): 524	Study design – letter