South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: TOCILIZUMAB FOR THE TREATMENT OF COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 26 November 2020; Update of first version (15 April 2020)

Key findings

- We updated the rapid review of clinical evidence for the use of tocilizumab with or without other medicines in the management of hospitalised patients with severe COVID-19 requiring oxygen or ventilatory assistance.
- We included one systematic review, 6 randomised controlled studies and one large cohort study in this update.
- In a meta-analysis of data from 5 randomised controlled trials, including 1325 participants, tocilizumab did not reduce mortality at 1 month (pooled risk ratio (RR) = 1.09 (95% CI 0.80 to 1.49, I^2 = 0%, moderate certainty evidence due to risk of bias associated with included RCTs) – 3 RCTs included death as part of a composite outcome.
- Tocilizumab may reduce the risk of mechanical ventilation (pooled RR = 0.71; 95% CI 0.52 to 0.96, I^2 = 0%, low certainty evidence) in four RCTs involving 771 patients. However, this may not be generalisable as high-flow nasal oxygen is preferred in clinical practice.
- The use of tocilizumab was not associated with an increased risk of harm.
- We did not identify any reports on the use of tocilizumab in children with COVID-19.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

	We recommend against the option and for the alternative (strong)	We suggest not to use the option or to use the alternative (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
Type of recommendation		X			

Recommendation: The sub-committee suggests that tocilizumab not be used for adults with COVID-19.
Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.
Rationale: Tocilizumab had no impact in mortality and there is uncertainty regarding the need for mechanical ventilation.
Level of Evidence: Low certainty evidence (based on the overall assessment for critical outcomes)
Review indicator: Evidence of safety and/or efficacy that is sufficient to change the recommendation.

Therapeutic Guidelines Sub-Committee for COVID-19: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen,), Andy Gray, Tamara Kredo, Renee De Waal, Gary Maartens, Jeremy Nel, Helen Rees.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available. It was noted that, as of 16 November 2020, 70 clinical trials investigating the role of TCZ in the management of COVID-19 are registered on https://clinicaltrials.gov/.

BACKGROUND

In patients infected with SARS-CoV-2, disease severity and outcomes are related to the characteristics of the immune response. [1-6] The median time from onset of symptoms of COVID-19 to the development of acute respiratory distress syndrome (ARDS) is as short as 8 days[7]. Interleukin (IL)-6 and other components of the inflammatory cascade play an important role in the inflammatory reaction and immune response[8]. However, excessive cytokine production ('cytokine storm') as part of a hyperinflammatory response has been suggested as a cause of severe COVID-19.[1-3] Controversy revolves around whether IL-6 is one of the most important cytokines involved in COVID-19-induced cytokine storms and if there is a correlation between elevated IL-6 levels in patients with COVID-19 and the risks of respiratory failure and the requirement for ventilation.[8, 9, 25]

Retrospective case series and individual case reports from China identified that IL-6 blockade therapy may constitute a novel therapeutic strategy in patients with severe SARS-CoV-2 pneumonia. [8, 10-13]

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody against human IL-6 receptor of immunoglobulin IgG1 subtype. In South Africa, it is registered for use in the management rheumatoid arthritis. TCZ specifically binds soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits the associated signal transduction. As a result, there is biological plausibility associated with TCZ's importance in the management COVID-19. [14] At the time of the first review, the safety and efficacy of TCZ and other IL-6 inhibitors in the management of COVID-19 had not yet been determined through randomised controlled trials[15]. Notwithstanding, TCZ had been recommended for use in seriously ill patients with elevated IL-6 by the *Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus* issued by *National Health Commission of China.*[8, 16] - a recommendation that has since been in conflict with other international treatment guidelines including those of the National Institutes of Health[17] and World Health Organisation[18].

With the recent publication of RCT data, the rapid review has been updated and focuses specifically on TCZ as it is the only IL-6 inhibitor commercially available in South Africa.

RESEARCH QUESTION:

Should tocilizumab be used for managing severe COVID-19 (with or without elevated IL-6 levels) in patients requiring oxygen or ventilatory assistance?

METHODS

This is an update of a rapid review conducted in April 2020. The original evidence search involved systematic searching of four electronic databases (PubMed as well as the Epistemonikos, Cochrane COVID Study Register and Living mapping and living network meta-analysis of COVID-19 studies databases).

For this update, the search strategy focused on randomised controlled trials and systematic reviews as such data had been published subsequent to the previous review. To this end, the Epistemonikos L*OVE evidence platform (https://app.iloveevidence.com/) was searched for randomised controlled trials and systemic reviews. Relevant records were extracted in a narrative table of results (see Table 1 below). One reviewer screened the records and extracted the data, while the second reviewer screened the records independently and checked the data extraction. Mismatches in abstract selection were settled by consensus. The search strategies for both reviews are shown in Appendix 2.

Eligibility criteria for review

Population: Patients with confirmed COVID-19 (with or without elevated IL-6 levels), no restriction to age but severe disease requiring oxygen or ventilatory assistance.

Intervention: Tocilizumab in combination with local standard of care at the time. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator).

Outcomes: Mortality; duration of ventilatory support including mechanical ventilation; duration of ICU stay; adverse reactions.

Study designs: Non-randomised cohorts, randomised controlled trials, and systematic reviews of studies in humans.

RESULTS

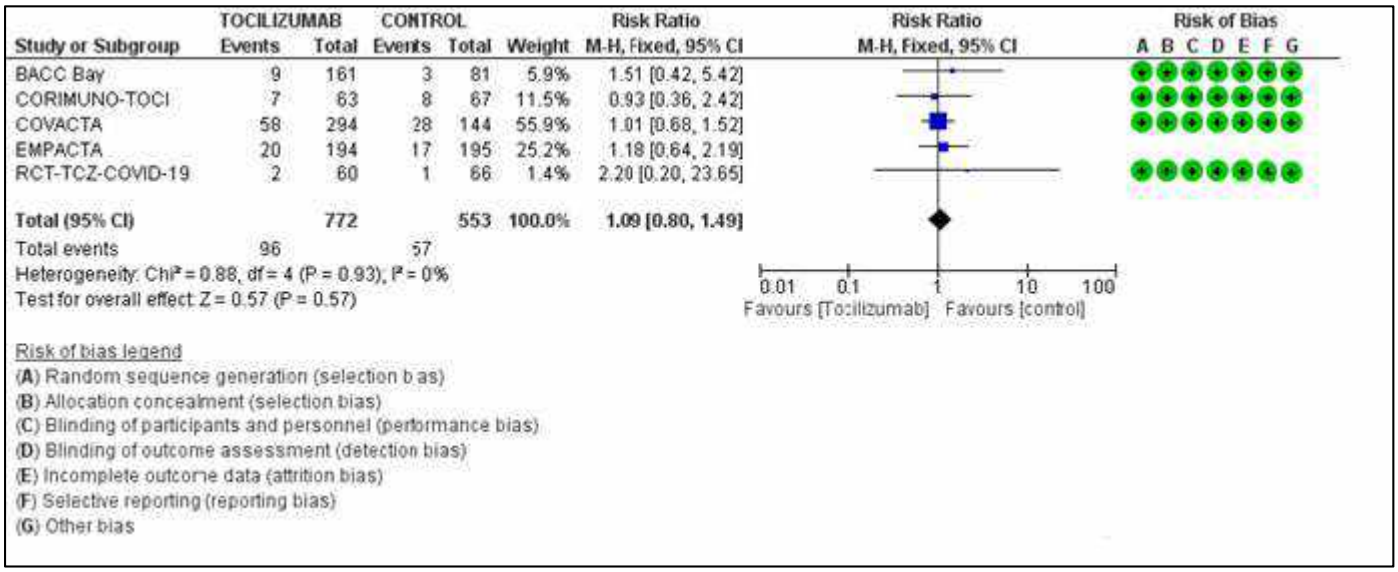
The Epistemonikos L*OVE evidence platform (https://app.iloveevidence.com/) were searched on 15 November 2020. Details of the search are provided in Appendix 2. One reviewer screened 58 records (10 RCTs and 48 systematic reviews). Six RCTs[19-24] and one systematic review[25] were identified as eligible for inclusion in this review. One additional study was found through reviewing the references cited in narrative reviews on this subject[26]. Although this latter study was a cohort study, considered to be of a lower level of evidence, it was included in the summary table on account of its population size. Data in **Table 1** report the main characteristics and outcomes of the included studies.

Systematic review[25]: 24 studies were included in this systematic review (5 RCTs and 19 cohorts), however, some concerns pertaining to the risk of bias assessment of the individual RCTs was noted. Of note is that RCTs either included "hyperinflammatory state" as a baseline patient inclusion criterion[20, 21], or majority of the patients in the tocilizumab cohort had elevated C-reactive protein levels[19, 22, 24]. These RCTs are described in the summary table below [19-23]. The outcomes of interest as per our PICO question in this systematic review are described below.

Randomised controlled trials:

- **Mortality (28 to 30 days)**
  - Five RCTs considered to be at low to moderate risk of bias
  - 1 325 patients
  - Pooled risk ratio (RR) = 1.09 (95% CI 0.80 to 1.49, I^2 = 0%)
  - Moderate certainty evidence downgraded due to imprecision (not reaching optimal information size for this outcome).
  - Three RCTs included death as part of a composite outcome measured on a clinical outcome scale[19, 21, 24].
  - Two RCTs[19, 21] were open-label and one RCT[21] was stopped early "for futility".
  - TCZ was administered intravenously at a dose of 8mg/kg to a maximum of 800mg. Some studies allowed for a repeat dose between 12 and 72 hours after the first dose if clinical signs and symptoms did not improve or worsened. The dosing schedules per RCT are detailed in the summary table below.

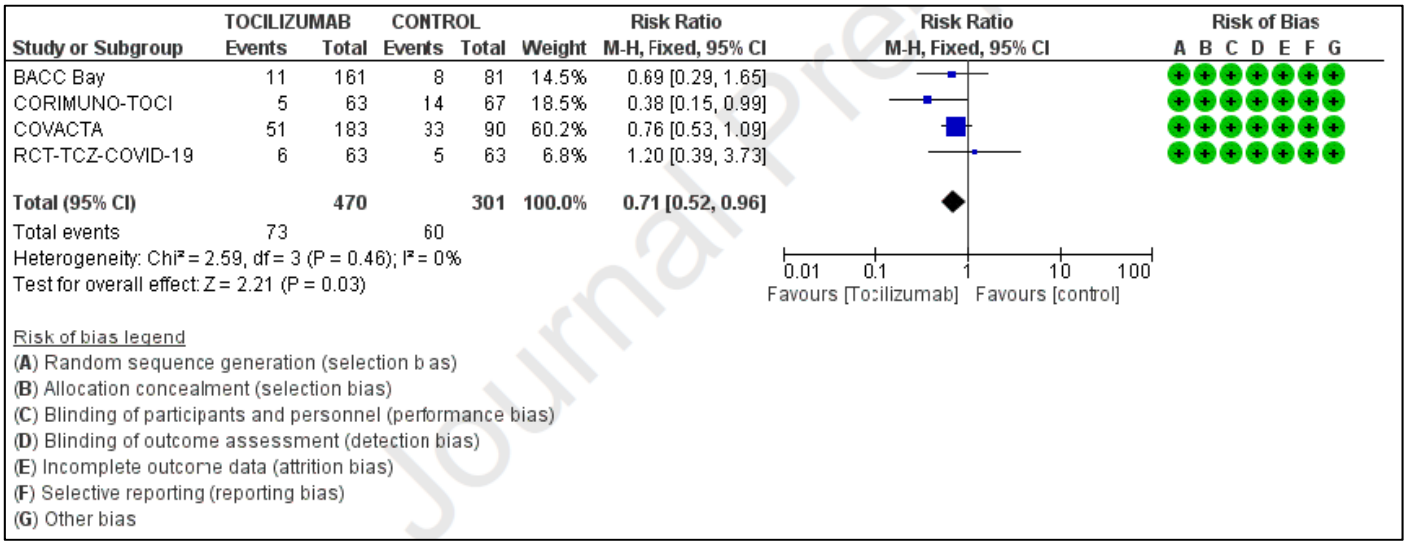
Figure 1: Forest plot for the effect of tocilizumab on 28-30 days mortality in randomised controlled trials with corresponding risk of bias



- **Risk of mechanical ventilation**
  - Four RCTs
  - 771 patients
  - Pooled RR = 0.71 (95% CI 0.52 to 0.96, I^2 = 0 %)
  - Corresponding NNT = 17 (95% CI 9 to 100)

- Low certainty evidence downgraded for imprecision (low number of events and small sample size) and for indirectness (small studies all from high income settings that may not be generalisable) – 2 RCTs[19, 21] were open-label and one RCT[21] was stopped early "for futility".
- Evidence is probably not applicable to the local setting, as high flow nasal oxygen is preferred in clinical practice, minimising the use of mechanical ventilation.

Figure 2: Forest plot for the effect of tocilizumab on risk for mechanical ventilation in randomised controlled trials with corresponding risk of bias [25]



- **Safety**

Data from the RCTs did not show higher risk of infections (Figure 3) or adverse events (Figure 4) with tocilizumab [pooled RR 0.63 (95% CI 0.38-1.06, 5 RCTs) and 0.83 (95% CI 0.55-1.24, 5 RCTs), respectively]

Figure 3: Forest plot for relative risk of infections with tocilizumab vs. control in randomised controlled trials [25]

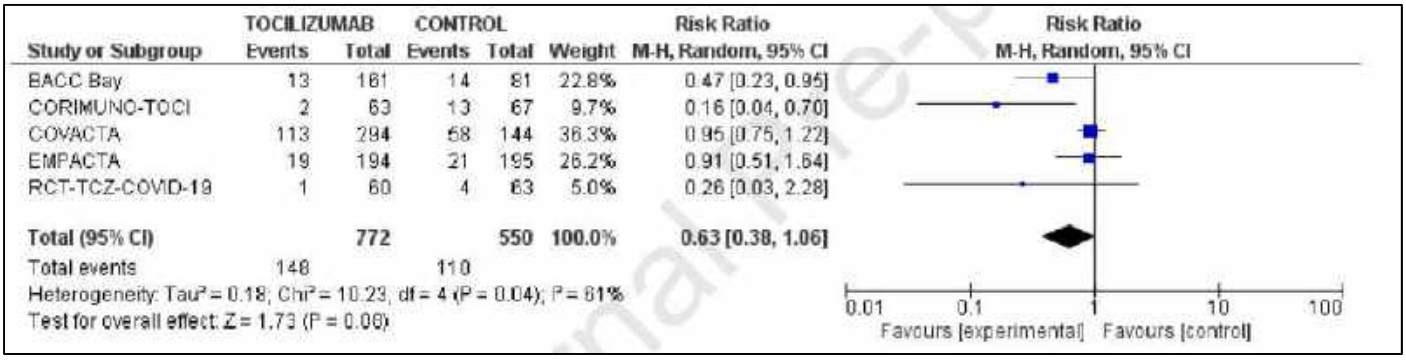
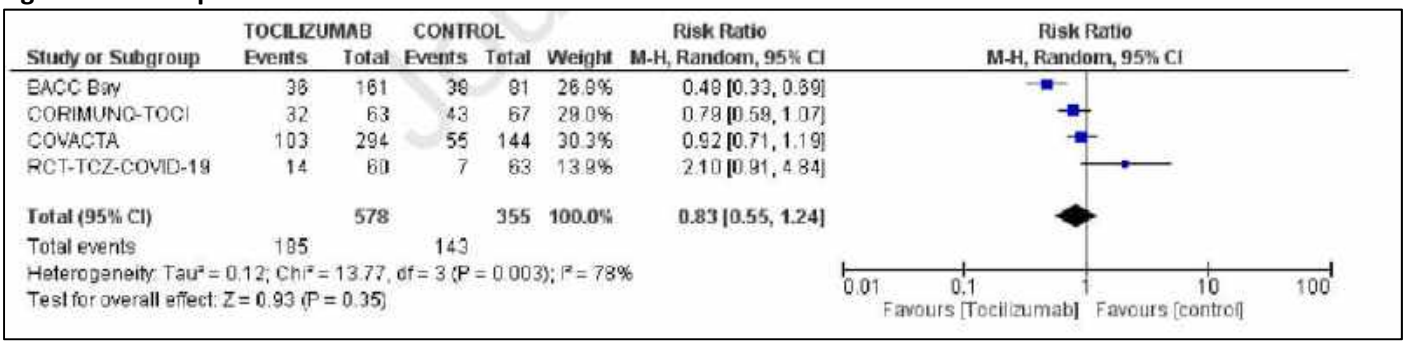


Figure 4: Forest plot for relative risk of adverse events with tocilizumab vs. control in randomised controlled trials [25]



Cohort studies

The systematic review also included 18 cohort studies (n=9850). Pooling this data from 9850 study participants produced an adjusted RR for mortality of 0.58 (95% CI 0.51 to 0.66, I^2= 2.5%). The overall quality of evidence was assessed as low (with a moderate risk of study bias, low risk of publication bias, direct evidence, low inconsistency, and precise estimate). However, generally there are concerns of confounding and selection bias with observational studies.

CONCLUSION

The systematic review reported no difference to mortality at 28 days (moderate certainty evidence). However, there is a suggestion that tocilizumab may reduce the risk of mechanical ventilation in hospitalized COVID-19 patients (low certainty evidence).

Currently available evidence remains insufficient to support the use of tocilizumab in the management of COVID-19 in South Africa outside of the clinical trial setting.

Reviewers: Roger Wiseman, Marc Blockman.

Declaration of interests: RW (Liberty Health (Pty) Ltd, South Africa), MB (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town) have no interests to declare in respect of tocilizumab therapy for COVID-19.

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Table 1. Characteristics of included studies

Systematic Review

Citation	Study design	Population (n)	Treatment	Main findings
Published peer reviewed Tleyjeh IM, Kashour Z, Damlaj M, et. al. [25] Efficacy and safety of tocilizumab in COVID-19 patients: A living systematic review and meta-analysis, Clinical Microbiology and Infection, 2020. DOI: 10.1016/j.cmi.2020.10.036.	Systematic review and meta-analysis of 5 RCTs and 19 cohort studies.	As for individual trials (RCT summarized above)	Intravenous tocilizumab (8mg/kg infusion, maximum 800mg). Some studies allowed for a repeat dose between 12 and 72 hours after the first dose if clinical signs and symptoms did not improve or worsened. **Dosing details per RCT:** Salvarani et. al[21]: 8 mg/kg up to a maximum of 800 mg, followed by a second dose after 12 hours Hermine et al.[19]: 8 mg/kg on day 1 and on day 3 if clinically indicated Stone et al.[20]: Single dose of tocilizumab 8 mg/kg (to a maximum of 800mg) Rosas et. al.[24]: 8 mg/kg infusion, maximum 800 mg second infusion could be administered 8 e24 hours after the first Salama et. al.[22]: 8 mg/kg X 1, Possible second dose	**Mortality (28 to 30 days)** o Five RCTs considered to be at low risk of bias o 1 325 patients o Pooled risk ratio (RR) = 1.09 (95% CI 0.80 to 1.49, I^2 = 0%) o Moderate certainty evidence downgraded due to imprecision (not reaching optimal information size for this outcome). **Risk of mechanical ventilation** o Four RCTs o 771 patients o Pooled RR = 0.71 (95% CI 0.52 to 0.96, I2 = 0 %) o Corresponding NNT = 17 (95% CI 9 to 100) o Low certainty evidence downgraded for imprecision (low number of events and small sample size) and for indirectness (small studies all from high income settings that may not be generalizable to our setting).

Controlled trials

Citation	Study design	Population (n)	Treatment	Main findings
Published, peer reviewed Hermine O, Mariette X, Tharaux PL, et al. for the CORIMUNO-19 Collaborative Group.[19]	Randomised, open-labelled, multicenter study. 31 March 2020 to 18 April 2020.	Setting: France, 9 university hospitals Patients: patients with COVID-19 and moderate or severe pneumonia requiring at least 3 L/min of oxygen	Patients were randomized on a 1:1 ratio to receive TCZ plus usual care or usual care alone. TCZ was administered at a dose of 8mg/kg IV on Day 1, followed by a fixed dose of 400mg IV on day 3 if the oxygen	Primary outcomes were scores higher than 5 on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS) on day 4 and survival without need of

Citation	Study design	Population (n)	Treatment	Main findings
JAMA internal medicine. 2020. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial		but without ventilation or ICU admission. Sample size: 130 (TCZ = 63 Usual Care = 67) Median age = TCZ = 64.0 years; UC = 63.3 years.	requirement has not decreased by more than 50%.	ventilation (including non-invasive ventilation) at day 14. Outcomes amended on 06 April 2020 to include high-flow oxygen in noninvasive ventilation. Primary: 12 patients (19%) had a WHO-CPS score greater than 5 at day 4 vs 19 (28%) in the UC group (median posterior absolute risk difference [ARD] −9.0%; 90% credible interval [CrI], −21.0 to 3.1) At day 14, 12% (95% CI −28%to 4%) fewer patients needed non-invasive ventilation (NIV) or mechanical ventilation (or died in the TCZ group than in the UC group (24%vs 36%, median posterior hazard ratio [HR] 0.58; 90% CrI, 0.33-1.00). The number of patients with mechanical ventilation or death at Day 14 was 11 (17%) and 18 (27%) in the TCZ and UC groups respectively.
Published, peer reviewed Stone JH, Frigault MJ, Serling-Boyd NJ, et al.[20] New England Journal of Medicine. 2020. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19 https://www.nejm.org/doi/full/10.1056/NEJMoa2028836	Randomised, double-blind, placebo controlled. 20 April 2020 to 15 June 2020.	Setting: USA, 7 hospitals in Boston Patients: patients with COVID-19 confirmed either by PCR or serum IgM antibody assay. Patients had to have at least two of the following signs: fever (body temperature >38°C) within 72 hours before enrollment, pulmonary infiltrates, or a need for supplemental oxygen to maintain an oxygen saturation > 92%. At least one of the following laboratory criteria also had to be fulfilled: a CRP > 50 mg/L, ferritin > 500 ng/ml, D-dimer > 1000 ng/ml, LDH > 250 U/L.	Patients were randomised on a 2:1 ratio to receive standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight administered intravenously, not to exceed 800 mg) or placebo Antiviral therapy, hydroxychloroquine, and glucocorticoids were permitted as concomitant treatment. However, some patients received remdesivir as concomitant treatment due to the release of the ACTT-1 trial during this trial. no patients received dexamethasone as the RECOVERY trial results were announced afterwards.	The primary outcome was intubation (or death, for patients who died before intubation) after administration of tocilizumab or placebo. The secondary endpoints were clinical worsening and discontinuation of supplemental oxygen among patients who had been receiving it at baseline. The hazard ratio for intubation or death for TCZ as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; P = 0.64). The hazard ratio for disease worsening was 1.11 (95% CI, 0.59 to 2.10; P = 0.73). At 14 days, 18.0% of the

Citation	Study design	Population (n)	Treatment	Main findings
		Sample size: 242 (TCZ = 161, Placebo = 81) Median age = 59.8 years (range 21.7 to 85.4 years).		patients in the TCZ group and 14.9% of the patients in the placebo group had demonstrated disease worsening. There was no difference in the median time to discontinuation of supplemental oxygen [TCZ = 5.0 days (95% CI, 3.8 to 7.6) vs placebo = 4.9 days (95% CI, 3.8 to 7.8)] in the placebo group (P = 0.69). At 14 days, 24.6% of the patients in the tocilizumab group and 21.2% of the patients in the placebo group were still receiving supplemental oxygen.
Published, peer reviewed Salvarani C, Dolci G, Massari M, et al. [21] JAMA internal medicine. 2020. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial.	Prospective, open-label, randomized clinical trial 31 March 2020 to 11 June 2020. The primary aim was to evaluate the efficacy of early administration of tocilizumab vs standard therapy in the first 2 weeks following randomization.	Setting: Italy, 24 hospitals Patients: patients with COVID-19 confirmed by positive PCR and the presence of acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) ratio between 200 and 300 mm/Hg, an inflammatory phenotype defined by a temperature greater than 38°C during the last 2 days, and/or serum CRP ≥ 10mg/dL and/or CRP level increased to at least twice the admission measurement. Sample size: 126 (TCZ = 60, Standard Care = 66) Median age = 60.0 years (range 53.0 to 72.0 years).	The TCZ group received TCZ intravenously within 8 hours from randomization at a dose of 8mg/kg up to a maximum of 800 mg, followed by a second dose after 12 hours. The control arm received supportive care following the treatment protocols of each centre. All drugs were allowed except IL-1 blockers, Jak inhibitors, and tumor necrosis factor inhibitors.	Primary endpoint: clinical worsening within 14 days since randomization, defined by the occurrence of 1 of the following events, whichever occurred first: • Admission to ICU with mechanical ventilation • Death from any cause • PaO2/FIO2 ratio less than 150 mm Hg in 1 of the scheduled arterial blood gas measurements or in an emergency measurement, confirmed within 4 hours by a second examination 17 of 60 patients (28.3%) in the TCZ group and 17 of 63 (27.0%) in the standard care group showed clinical worsening within 14 days following randomization (rate ratio, 1.05; 95% CI, 0.59-1.86; P = .87)
Published, peer reviewed Gupta S, Wang W, Hayek SS, et. al for the STOP-COVID Investigators.[26]	Multi-centre cohort study 04 March 2020 to 10 May 2020.	Setting: USA, 64 hospitals Patients: Patients admitted to ICU with laboratory confirmed COVID-19 (detected by nasopharyngeal or oropharayngeal swab) where the ICU	No dose of TCZ is provided. Patients were categorized according to whether or not they received tocilizumab (either intravenously or subcutaneously) during the first 2 days of ICU admission. Patients who received tocilizumab after the first 2 days of ICU admission were	Primary endpoint: In-hospital death, censored at hospital discharge or last follow-up. After a median follow-up of 26 days for TCZ and 27 days for the non-TCZ group), a total

Citation	Study design	Population (n)	Treatment	Main findings
JAMA internal medicine. 2020. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. DOI: 10.1001/jamainternmed.2020.6252.		admission is directly attributable to COVID-19. Sample size: 3924 (Male = 2 464, Female = 1460) 433 patients were treated with TCZ within 2 days of ICU admission Median age = 62.0 years (IQR = 52.0 to 71.0 years).	categorized in the non-tocilizumab–treated group.	1544 patients (39.3%) died. Of these, death occurred in 125 of the 433 TCZ patients (28.9%) and 1419 of the 3491 non-TCZ patients (40.6%) (unadjusted HR, 0.64; 95% CI, 0.54-0.77). Adjusted risk of death for TCZ patients compared with non-TCZ patients was HR,0.71; 95% CI, 0.56-0.92). The estimated 30-day mortality was 27.5% (95% CI, 21.2%-33.8%) in the tocilizumab-treated patients and 37.1% (95%CI, 35.5%-38.7%) in the non-tocilizumab–treated patients (risk difference, 9.6%; 95%CI, 3.1%-16.0%).
Published, non-peer reviewed Salama C, Han J, Yau L, et. al. [22] medRxiv 2020. Tocilizumab in nonventilated patients hospitalized with Covid-19 pneumonia. DOI: 10.1101/2020.10.21.20210203	Randomised, double-blind, placebo controlled, Phase III study	Setting: Multi-centre study across 6 countries Patients: hospitalized patients with COVID-19 pneumonia confirmed by positive PCR test and radiographic imaging. Sample size: 377 (TCZ = 249, Placebo = 128) Median age (± SD) = TCZ = 56.0 ±14.3 years; placebo = 55.6 ±14.9 years.	Patients were randomized (2:1) to intravenous tocilizumab (8 mg/kg, maximum 800 mg) or placebo. If patients worsened or did not improve, an additional infusion could be administered 8 to 24 hours after the first. Both groups received standard care per local practice which could include antiviral treatment, limited systemic corticosteroids (≤1 mg/kg methylprednisolone or equivalent recommended) and supportive care In the tocilizumab and placebo arms, 55.4% and 67.2% of patients received dexamethasone, respectively, and 52.6% and 58.6% received remdesivir, respectively.	Primary endpoint: cumulative proportion of patients requiring mechanical ventilation (mechanical invasive ventilation or extracorporeal membrane oxygen) or who had died by Day 28. TCZ = 12.0% (95% CI, 8.52% to 16.86%) Placebo = 19.3 % (95% CI, 13.34% to 27.36%) (HR, 0.56 [95% CI, 0.33 to 0.97]; log-rank P=0.036).
Non-peer reviewed Wang D, Fu B, Peng Z, et. al. [24]	Randomized, controlled, open-label, multicentre trial	Setting: China, 6 hospitals in Anhui and Hubei	Patients were randomly assigned in a 1:1 ratio to receive either tocilizumab in addition to standard care, or standard care alone. If a patient in the control group progressed to	Primary endpoint: Cure rate. Cure was defined as 1) fever attenuated for continuously for 7 days, 2) two negative COVD-19 PCR tests, 3) CT scan showing

Citation	Study design	Population (n)	Treatment	Main findings
SSRN. 2020. Tocilizumab Ameliorates the Hypoxia in COVID-19 Moderate Patients with Bilateral Pulmonary Lesions: A Randomized, Controlled, Open-Label, Multicenter Trial. DOI: 10.2139/ssrn.3667681	13 February 2020 to 13 March 2020.	Patients: Patients PCR confirmed COVID-19 between the ages of 18 and 85 years, had elevated plasma IL-6 levels with moderate or severe disease. Moderate disease was defined as fever or other respiratory symptoms as well as bilateral pulmonary lesions confirmed on chest imaging Severe disease was defined as the presence of any of the following: 1) respiratory rate ≥30 breaths per min; 2) SpO2 ≤ 93% while breathing room air; and/or 3) PaO2/FiO2 ≤ 300 mmHg Sample size: 65 (TCZ = 33, Control = 1460) Median age = 63.0 years (IQR = 55.0 to 71.0 years).	severe disease within 3 days after randomization, they were transferred to the tocilizumab group.	absorption of chest effusion by more than 50% percent on discharge. The cure rate for TCZ was 94.12% vs 87.10% for the control group, but the difference was not statistically significant (P = 0.4133). For the secondary endpoints of recovery rate of hypoxia over 14 days and the worsening rate of hypoxia during hospitalization: Recovery rate of hypoxia: TCZ = 91.67% vs 60.00% (p = 0.0328) in the control group. The difference was evident from day 4 and statistically significant from day 12.
Published non-peer reviewed Rosas I, Bräu N, Waters M, et. al.[23] medRxiv 2020 Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. DOI 10.1101/2020.08.27.20183442	Randomized, double-blind, placebo-controlled trial	Setting: 9 Countries - Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK and USA. Patients: Patients with PCR confirmed COVID-19 and evidenced by bilateral chest infiltrates on chest x-ray or CT. Patients were also required to have blood oxygen saturation ≤93% or partial pressure of oxygen/fraction of inspired oxygen <300 mmHg. Sample size: 438 (TCZ = 294, Control = 144) Median age = 63.0 years (IQR = 55.0 to 71.0 years).	Patients were randomized (2:1) to receive intravenous tocilizumab (8 mg/kg infusion, maximum 800 mg) or placebo plus standard care. If clinical signs or symptoms did not improve or worsened a second infusion could be administered 8 to 24 hours after the first.	Primary endpoint: Clinical status assessed on a 7-category ordinal scale at day 28. Clinical status was measured at baseline and every day during hospitalization. Clinical status at day 28 was not statistically significantly improved for tocilizumab versus placebo (P=0.36). Median (95% CI) ordinal scale values at day 28: TCZ = 1.0 (1.0 to 1.0) for tocilizumab Placebo 2.0 (1.0 to 4.0) (odds ratio, 1.19 [0.81 to 1.76]). There was no difference in mortality at day 28 between tocilizumab (19.7%) and placebo (19.4%) (difference, 0.3% [95% CI, –7.6 to 8.2]; nominal P=0.94).

Citation	Study design	Population (n)	Treatment	Main findings
				Median time to hospital discharge was 8 days shorter with tocilizumab than placebo (20.0 and 28.0, respectively; nominal P=0.037; hazard ratio 1.35 [95% CI 1.02 to 1.79]). Median duration of ICU stay was 5.8 days shorter with tocilizumab than placebo (9.8 and 15.5, respectively; nominal P=0.045).

Appendix 1: GUIDELINE CONSIDERATIONS

1. NIH COVID-19 Treatment Guidelines (updated August 27, 2020)[17]

Interleukin-6 Inhibitors

Recommendation: The Panel recommends against the use of anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab) for the treatment of COVID-19, except in a clinical trial (BI)**.**

Rationale: Preliminary, unpublished data from randomized, controlled trials failed to demonstrate efficacy of sarilumab or tocilizumab in patients with COVID-19. There are only limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19.

2. World Health Organization: Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected. Interim guidance (27 May 2020)[18]:

Antivirals, immunomodulators and other adjunctive therapies for COVID-19

Recommendation: We recommend that the following drugs not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials:

- Chloroquine and hydroxychloroquine (+/- azithromycin)
- Antivirals, including but not limited to:
  - Lopinavir/ritonavir
  - Remdesivir
  - Umifenovir
  - Favipiravir
- Immunomodulators, including but not limited to:
  - Tocilizumab
  - Interferon-β-1a
- Plasma therapy

3. Australian guidelines for the clinical care of people with COVID-19. Version 28.0 (updated 13 August 2020)[27]

6.6.23 Tocilizumab

Recommendation: Do not use tocilizumab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Appendix 2: Search strategy

Search Strategy 1:
Date: 11 April 2020
Period: Prior to 11 April 2020

Epistemonikos

(title:(coronavirus or covid* or 2019-ncov or sars-cov-2) or abstract:(coronavirus or covid* or 2019-ncov or sars-cov-2)) and (title:(tocilizumab or IL-6 inhibitor or interleukin-6 inhibitor) or abstract:(tocilizumab or IL-6 inhibitor or interleukin-6 inhibitor))

Records retrieved: 13 (1 relevant to PICO question)

PubMed

(((coronavirus[title/abstract] or covid*[title/abstract] or 2019-ncov[title/abstract] or sars-cov-2[title/abstract])) and (tocilizumab[title/abstract] or IL-6 inhibitor[title/abstract] or interleukin-6 inhibitor[title/abstract]) not ((animals[mh] not humans[mh]))) and ("2019/12/01"[date - publication] : "3000"[date - publication])

Records retrieved: 43 (1 relevant to PICO question)

Living mapping and living network meta-analysis of COVID-19 studies (https://covid-nma.com/)

Tocilizumab
Interleukin-6 inhibitor
Interleukine-6 inhibitor

Records retrieved: none

Cochrane COVID Study Register (https://covid-19.cochrane.org/)

Tocilizumab AND interleukin-6 inhibitor

Records retrieved: 12 (none relevant to PICO question)

Search Strategy 2:
Date: 15 November 2020

Epistemonikos L*OVE evidence platform:

Tocilizumab

Records retrieved: 58 (10 RCTs and 48 systematic reviews). 6 RCTs and 1 systematic review were included for review.

Appendix 3: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐ Uncertain ☐	There was no difference in risk of mortality at 28 or 30 days. The NNT to prevent one additional patient being mechanical ventilated was 17 with wide 95% CI 9 - 100.[24]
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒ Uncertain ☐	No increased risk of infections or adverse events was observed with tocilizumab use in the RCTs [24]
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒	There are no definitive outcome data reflecting a mortality benefit associated with the use of tocilizumab in this clinical setting (see narrative above).
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	The certainty of evidence is low based on the evidence from critical outcomes such as mortality, need for ventilation and adverse events (see narrative above).
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	Tocilizumab is SAHPRA registered, but the recommendation is not to support the use of tocilizumab in this indication.
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☒	Price of medicines/dose: **Medicine** | **Price - SEP** Tocilizumab 480mg^ | R 7 014.23 Tocilizumab 600mg# | R 8 767.79 Tocilizumab 800mg* | R 11 690.38* ^ dose for a 60kg patient # Dose for a 75kg patient * Maximum dose **Single exit price (SEP), ex manufacturer:** 400mg/20ml = R 5 845.19; 200mg/10ml = R 2 922.60; 80mg/4ml = R 1 169.04 *Source*: SEP database, March 2020 - https://medicineprices.org.za/
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☐ Major ☐ Uncertain ☒ **Is the option acceptable to key stakeholders?** Yes ☐ No ☐ Uncertain ☒	

Version	Date	Reviewer(s)	Recommendation and Rationale
First	15 April 2020	RW, MB	Recommend against using tocilizumab in children or adult patients with COVID-19 as there is currently insufficient evidence to recommend routine use - consider in context of clinical trial setting.
Second	17 November 2020	RW, MB	Recommend against using tocilizumab in children or adult patients with COVID-19 as there is currently insufficient RCT evidence to recommend routine use - consider in context of clinical trial setting.