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

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

**Date: 6 April 2022 (fourth update of the initial 15 April 2020 rapid review)**

## 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 identified 12 randomised controlled trials (RCTs), and a systematic review and meta-analysis that combined all 12 RCTs.
- Overall tocilizumab reduced all-cause mortality from 29.2% to 25.7% at 28 days: The absolute risk reduction was 3.5% (95% confidence interval (CI) 1.5% to 5.6%), and the relative risk (RR) 0.88 (95% CI 0.81 to 0.95, 11 RCTs, n = 6 937). The number needed to treat to prevent one additional death was 29 (95% CI 18 to 67).
- Tocilizumab was not associated with an increased risk of adverse events (RR 1.23; 95% CI 0.93 to 1.62), or serious adverse events (RR 0.92; 95% CI 0.77 to 1.08).
- We did not identify any reports on the use of tocilizumab in children with COVID-19.
- For use of tocilizumab in pregnancy, refer to Addendum A.

**NEML MAC ON COVID-19 THERAPEUTICS 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 not to use tocilizumab. Despite the reduction in death in the included trials, tocilizumab is not affordable at the current offered price.

*Rationale:* A meta-analysis of 11 randomised controlled trials reporting mortality showed that tocilizumab, used in combination with corticosteroids, reduced all-cause mortality at day 28 from 29.2% to 25.7% amongst adult patients with COVID-19 with hypoxia and evidence of systemic inflammation (CRP ≥ 75mg/L), without an increase in clinically significant adverse events. However, the sub-committee expressed concerns regarding the budget impact and national supply of tocilizumab.

**Level of Evidence: I High to moderate certainty evidence**

***Review indicator:*** **Reduction in price**

**NEMLC MAC on COVID-19 Therapeutics:** Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, 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 7 April 2022, 42 clinical trials investigating the role of tocilizumab in the management of COVID-19 are registered on the International Clinical Trials Registry Platform (ICTRP), accessed from https://covid-nma.com/

| 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. |
| Third | 5 March 2021 | RW, MB, RdW, KC | Suggest the use of tocilizumab in hospitalized hypoxic adult patients with COVID-19 and a CRP ≥ 75mg/L, but with concerns about affordability and possible supply constraints. |
| Fourth | 20 May 2021 | RW, MB | No change |

| | | | |
|---|---|---|---|
| Fifth | 6 April 2022 | RW, MB | Addendum A added providing information for use of tocilizumab in pregnancy |

## 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 hyper-inflammatory response has been suggested as a cause of severe COVID-19.[1-3] There has been some controversy as to whether IL-6 constitutes 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 the only commercially available IL-6 inhibitor and is registered for use in the management rheumatoid arthritis. Tocilizumab 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 tocilizumab's importance in the management COVID-19. [14] However, the World Health Organization guideline provides no guidance on the use of tocilizumab currently, while the Australian and US National Institutes of Health (NIH) guidelines do allow for its use in patients who are within 24 hours of admission to the intensive care unit (ICU) and require invasive or noninvasive mechanical ventilation or high-flow oxygen (Appendix 1).

Existing RECOVERY RCT data was recently published in a peer-reviewed journal, thus warranting an update of this rapid review.

## 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 the fourth iteration of this rapid review. The initial review was conducted in April 2020, for which we systematically searched 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).

The search strategy for the first update focused on randomised controlled trials and systematic reviews as such data had been published subsequent to the initial 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 update of 26 November 2020).

The second update focused on new studies published after 15 November 2020. The Epistemonikos L*OVE evidence platform (https://app.iloveevidence.com/) was searched for randomised controlled trials and systemic reviews (see update of 15 April 2021).

This third update was triggered on account of the formal publication of the RECOVERY trial[32] data for tocilizumab in a peer-reviewed journal. The Living Mapping and Living Network Meta-Analysis of COVID-19 studies (https://covid-nma.com/) platform was searched on 18 May 2021 to identify updates to the living meta-analysis for tocilizumab versus standard of care. Relevant records were extracted and summarized in a narrative table of results (see Table 1).

The search strategies for all four 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; progression to ICU admission, progression to mechanical ventilation, clinical outcome on an ordinal scale at chosen time points, adverse events, adverse reactions.

Study designs: Randomised controlled trials, and systematic reviews of studies in humans.

## RESULTS

The previous version of this review included 9 RCTs found during a search of the Epistemonikos L*OVE evidence platform (https://app.iloveevidence.com/). Details of the search are provided in Appendix 2. The Cochrane supported living meta-analysis (COVID-NMA)[29] was recently updated to include two additional RCTs[33, 34] as well as the published, peer-reviewed RECOVERY paper in the Lancet.[32] Findings of this living meta-analysis for the outcomes of interest are detailed below in Table 1. The associated forest plots are included in Appendix 3. The main characteristics and outcomes of the 12 included RCTs are summarised in Table 2.

**All-cause mortality at day 28**

The COVID-NMA meta-analysis showed that tocilizumab 8mg/kg compared with standard of care/placebo for Mild/Moderate/Severe/Critical COVID-19 (eleven RCTs, 6 937 participants) reduced mortality: RR 0.88 (95% CI 0.81 to 0.95; $I^2$=0.0%).

In Horby *et al.* (the Recovery trial)[32] there was some evidence for effect modification by concomitant use of steroids (Chi squared test for interaction p=0.01). In participants that received corticosteroids, day 28 mortality was 29% (482/1644) in the tocilizumab arm and 35% (600/1721) in the usual care arm. Amongst participants that did not receive corticosteroids, day 28 mortality was 39% (139/357) in the tocilizumab arm and 35% (127/367) in the usual care arm.

**WHO ordinal progression score level 7 or above at Day 28**

Level 7 and above on the WHO ordinal scale for clinical improvement is defined as "hospitalized patients with severe disease requiring mechanical ventilation ± additional organ support (ECMO, vasopressors or dialysis) OR death"[30].
COVID-NMA meta-analysis showed that tocilizumab 8mg/kg compared with standard of care/placebo for mild/moderate/severe/critical COVID-19 (four RCTs, 1 066 participants) reduced progression to WHO level 7 or above: RR 0.88 (95% CI 0.59 to 1.32; $I^2$=65.3%).

**Adverse events**

Tocilizumab 8mg/kg (except for Wang *et. al.* which allowed for a standard 400 mg dose) compared with standard of care/placebo for mild/moderate/severe/critical COVID-19 (eight RCTs, 1 714 participants): the included studies showed no statistically significant difference in adverse events: RR 1.23 (95% CI 0.93 to 1.62; $I^2$=81.3%).

**Serious adverse events**

Tocilizumab 8mg/kg (except for Wang *et al.* which allowed for a standard 400 mg dose) compared with standard of care/placebo for mild/moderate/severe/critical COVID-19 (ten RCTs, 2 532 participants): the included studies showed no statistically significant difference in serious adverse events: RR 0.92 (95% CI 0.77 to 1.08; $I^2$=0.0%).

**Table 1: Summary of findings of the Cochrane Living Meta-analysis: Tocilizumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19 [29]**

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with Standard care/Placebo | Risk with Tocilizumab | | | |
| Clinical improvement D28 [b] | 536 per 1000 | **569 per 1000** (531 to 601) | **RR 1.06** (0.99 to 1.12) | 5625 (8 RCTs) [c] | ⨁⨁⨁◯ MODERATE [d] |
| WHO progression score (level 7 or above) D28 | 279 per 1000 | **246 per 1000** (165 - 369) | **RR: 0.88** (0.59 - 1.32) | 1066 (4 RCTs) [e] | ⨁⨁◯◯ LOW [f,g] |
| All-cause mortality D28 | 292 per 1000 | **257 per 1000** (237 to 278) | **RR: 0.88** (0.81 - 0.95) | 6937 (11 RCTs) [h] | ⨁⨁⨁⨁ HIGH [i] |
| All-cause mortality D60 or above | 133 per 1000 | **114 per 1000** (70 to 186) | **RR 0.86** (0.53 to 1.40) | 519 (2 RCTs) [j] | ⨁⨁◯◯ LOW [k,l] |
| Adverse events | 429 per 1000 | **527 per 1000** (399 to 695) | **RR 1.23** (0.93 to 1.62) | 1714 (8 RCTs) [m] | ⨁◯◯◯ VERY LOW [n,o,p] |
| Serious adverse events | 147 per 1000 | **136 per 1000** (113 to 159) | **RR 0.89** (0.75 to 1.06) | 2532 (10 RCTs) [q] | ⨁⨁⨁◯ MODERATE [n] |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

## CONCLUSION

A systematic review of twelve RCTs of the use of tocilizumab in hospitalized patients with COVID-19 demonstrated a reduction in all-cause mortality at day 28. The absolute risk reduction was 3.5% (95% CI 1.5% to 5.6%), while the relative risk was 0.88 (95% CI 0.81 to 0.95, 11 RCTs reporting mortality, n = 6 937). The number needed to treat to prevent one additional death due to COVID-19 was calculated as 29 (95% CI 18 to 67). This result is largely driven by the findings of the RECOVERY trial[32] wherein tocilizumab, when used for hypoxic patients with a CRP of >75mg/L, produced a 4% absolute reduction in 28-day mortality compared with standard of care alone (TCZ = 31% vs. SOC = 35%; RR 0.85; 95% CI, 0.76 to 0.94; p=0·0028). However, there are concerns regarding the national supply of tocilizumab and that the product is unaffordable. On this basis, it is recommended that tocilizumab, used in combination with corticosteroids, not be included in the COVID-19 treatment guidelines for the management of hospitalized hypoxic SARS-CoV-2 infected patients with CRP levels >75mg/L.

**Reviewers:** Roger Wiseman (Liberty Health (Pty) Ltd, South Africa), Marc Blockman (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town).

**Additional reviewers**: Karen Cohen (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town). Renee De Waal (Centre for Infectious Disease Epidemiology and Research, University of Cape Town).

**Declaration of interests:** RW, MB, KC and RdW have no interests to declare in respect of tocilizumab.

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**Table 2. Characteristics of 12 randomised controlled trials included in the Cochrane living systematic review**

| Citation | Study design | Population (n) | Treatment | Main findings | Comments |
|---|---|---|---|---|---|
| Published, not peer-reviewed<br><br>Gordon AC, Mouncey PR, Al-Beidh F, et. al. for the REMAP-CAP Investigators.[28]<br><br>Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report:<br><br>medRxiv 2020.<br><br>DOI: 10.1101/2021.01.07.21249390<br><br>NCT02735707 | Randomised, placebo controlled multifactorial open-label trial. Study is ongoing.<br><br>Primary endpoint: composite outcome of mortality or respiratory and CVS organ support-free days up to day 21 in survivors<br><br>This analysis includes participants enrolled up to 19 November 2020 | Multicentre: 113 sites across 6 countries.<br><br>Participants: Critically ill adult patients with suspected or confirmed Covid-19, admitted to an intensive care unit (ICU) and receiving respiratory or cardiovascular organ support. Patients were randomized receive therapy within 24 hours of commencing organ support in an intensive care unit.<br><br>Population:<br>895 were assigned to the immune modulation therapy domain (TCZ 366, sarilumab 48, 69 "other interventions", 412 control). 30 participants withdrew consent, and 11 had missing primary outcome data<br><br>803 participants were included at baseline (TCZ = 353, sarilumab = 48, control = 402)<br><br>Outcomes for participants in the Other treatment arm were not reported on separately.<br><br>The following participant numbers were included in the mortality analysis: | TCZ was administered intravenously at a dose of 8mg/kg up to a maximum of 800 mg. This dose could be repeated 12 - 24 hours later at the discretion of the treating clinician. 92% of participants received at least one dose of TCZ and 29% received a second dose.<br>707 participants were enrolled after the dexamethasone result from the RECOVERY trial. Of these participants, 93.3% (610/654) were treated with corticosteroids at enrollment or within the following 48 hours. Of the 158 participants recruited before June 17, 107 were randomized in the previously published Corticosteroid domain within REMAP-CAP, 41 allocated to a seven-day course of hydrocortisone and 39 to shock dependent hydrocortisone.<br><br>Remdesivir use was recorded in 32.8% of participants. | Primary outcome: Respiratory and cardiovascular organ support-free days up to day 21. In this composite ordinal outcome, all deaths within hospital are assigned the worst outcome (–1). Among survivors, respiratory and cardiovascular organ support-free days are calculated up to day 21, such that a higher number represents faster recovery.<br><br>Hospital mortality was 28.0% (98/350) for TCZ, 22.2% (10/45) for SRL and 35.8% (142/397) for control. Compared with control, median adjusted odds ratios for hospital survival were 1.64 (95% CrI 1.14, 2.35) for TCZ and 2.01 (95% CrI 1.18, 4.71) for SRL.<br><br>Median organ support-free days were 10 (IQR -1, 16), 11 (IQR 0, 16) and 0 (IQR -1, 15) for TCZ, SRL and control groups, respectively. Compared with control, median adjusted odds ratios were 1.64 (95% CrI 1.25, 2.14) for TCZ and 1.76 (95% CrI 1.17, 2.91) for SRL. | Risk of bias assessment: MODERATE with some concerns noted.<br>It was an unblinded study.<br>There appears to be missing data regarding the concomitant use of dexamethasone and remdesivir.<br>Although treatment assignment was adjusted for in their model, it's not clear if/how dexamethasone was adjusted for once it became standard of care.<br>It appears that some participants were included in the final analysis despite having missing outcome data. It's not clear how these participants were censored. |

| Citation | Study design | Population (n) | Treatment | Main findings | Comments |
|---|---|---|---|---|---|
| | | TCZ = 350<br>SRL = 45<br>Control = 397<br><br>Median age: 61.4 years<br>(TCZ = 61.5 years; SRL = 63.4 years; placebo = 61.1 years | | | |
| Published, peer reviewed<br><br>Salvarani C, Dolci G, Massari M, et al. [21]<br><br>JAMA internal medicine. 2020.<br><br>Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial.<br><br>NCT04346355 | Prospective, open-label, randomized clinical trial<br><br>31 March 2020 to 11 June 2020.<br><br>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<br><br>Participants: 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.<br><br>Sample size: 126 (TCZ = 60, Standard Care = 66)<br><br>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.<br><br>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:<br>• Admission to ICU with mechanical ventilation<br>• Death from any cause<br>• 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<br><br>17 of 60 participants (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) | Risk of bias assessment: **MODERATE** with some concerns noted. ITT analysis, but an unblinded study with a cross-over design (21.2% of patients in the SOC arm received study treatment due to clinical worsening). |
| Published, non-peer reviewed<br><br>Salama C, Han J, Yau L, et. al. [22]<br><br>medRxiv 2020. | Randomised, double-blind, placebo controlled, Phase III study | Setting: Multi-centre study across 6 countries<br><br>Participants: hospitalized patients with COVID-19 pneumonia confirmed by positive PCR test and radiographic imaging. | Participants were randomized (2:1) to intravenous tocilizumab (8 mg/kg, maximum 800 mg) or placebo. If participants worsened or did not improve, an additional infusion could be administered 8 to 24 hours after the first. | Primary endpoint: cumulative proportion of participants requiring mechanical ventilation (mechanical invasive ventilation or extracorporeal membrane oxygen) or who had<br>died by Day 28. | Risk of bias assessment: **LOW** as study was double-blind, placebo-controlled with random allocation sequence and adequate concealment. Data was available for >95% of population and outcomes reported were pre-specified in the protocol. |

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| Tocilizumab in non-ventilated patients hospitalized with Covid-19 pneumonia.<br><br>DOI: 10.1101/2020.10.21.20210203<br><br>NCT04372186 | | Sample size: 377 (TCZ = 249, Placebo = 128)<br><br>Median age (± SD) = TCZ = 56.0 ±14.3 years; placebo = 55.6 ±14.9 years. | 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<br><br>In the tocilizumab and placebo arms, 55.4% and 67.2% of participants received dexamethasone, respectively, and 52.6% and 58.6% received remdesivir, respectively. | TCZ = 12.0% (95% CI, 8.52% to 16.86%) Placebo = 19.3 % (95% CI, 13.34% to 27.36%)<br>(HR, 0.56 [95% CI, 0.33 to 0.97]; log-rank P=0.036). | |
| Published, peer reviewed<br><br>Hermine O, Mariette X, Tharaux PL, et al. for the CORIMUNO-19 Collaborative Group.[19]<br><br>JAMA internal medicine. 2020.<br><br>Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial<br><br>NCT04331808 | Randomised, open-labelled, multicenter study.<br><br>31 March 2020 to 18 April 2020. | Setting: France, 9 university hospitals<br><br>Participants: patients with COVID-19 and moderate or severe pneumonia requiring at least 3 L/min of oxygen but without ventilation or ICU admission.<br><br>Sample size: 130 (TCZ = 63 Usual Care = 67)<br><br>Median age = TCZ = 64.0 years; UC = 63.3 years. | Participants 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 requirement has not decreased by more than 50%. | 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 ventilation (including non-invasive ventilation) at day 14.<br><br>Outcomes amended on 06 April 2020 to include high-flow oxygen in noninvasive ventilation.<br><br>Primary: 12 participants (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)<br><br>At day 14, 12% (95% CI −28%to 4%) fewer participants 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). | Risk of bias assessment: **MODERATE** as this was an unblinded study. |

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| | | | | The number of participants with mechanical ventilation or death at Day 14 was 11 (17%) and 18 (27%) in the TCZ and UC groups respectively. | |
| Published, peer reviewed<br><br>Stone JH, Frigault MJ, Serling-Boyd NJ, et al.[20]<br><br>New England Journal of Medicine. 2020.<br><br>Efficacy of Tocilizumab in Patients Hospitalized with Covid-19<br><br>https://www.nejm.org/doi/full/10.1056/NEJMoa2028836<br><br>NCT04356937 | Randomised, double-blind, placebo controlled.<br><br>20 April 2020 to 15 June 2020. | Setting: USA, 7 hospitals in Boston<br><br>Participants: patients with COVID-19 confirmed either by PCR or serum IgM antibody assay. Participants 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.<br><br>Sample size: 242 (TCZ = 161, Placebo = 81)<br><br>Median age = 59.8 years (range 21.7 to 85.4 years). | Participants 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<br><br>Antiviral therapy, hydroxychloroquine, and glucocorticoids were permitted as concomitant treatment. However, some participants received remdesivir as concomitant treatment due to the release of the ACTT-1 trial during this trial. no participants received dexamethasone as the RECOVERY trial results were announced afterwards. | The primary outcome was intubation (or death, for participants who died before intubation) after administration of tocilizumab or placebo.<br><br>The secondary endpoints were clinical worsening and discontinuation of supplemental oxygen among participants who had been receiving it at baseline.<br><br>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 participants in the TCZ group and 14.9% of the participants 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 participants in the tocilizumab group and 21.2% of the participants in the placebo group were still receiving supplemental oxygen. | Risk of bias assessment: **LOW** as the study is a randomized, double-blind, placebo-controlled trial with random allocation sequence and adequate concealment. 242/243 patients analyzed (<5% of total sample size). |

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| Non-peer reviewed<br><br>Wang D, Fu B, Peng Z, et. al.[24]<br><br>SSRN. 2020.<br><br>Tocilizumab Ameliorates the Hypoxia in COVID-19 Moderate Patients with Bilateral Pulmonary Lesions: A Randomized, Controlled, Open-Label, Multicenter Trial.<br><br>DOI: 10.2139/ssrn.3667681<br><br>ChiCTR2000029765 | Randomized, controlled, open-label, multicentre trial<br><br>13 February 2020 to 13 March 2020. | Setting: China, 6 hospitals in Anhui and Hubei<br><br>Participants: Patients PCR confirmed COVID-19 between the ages of 18 and 85 years, had elevated plasma IL-6 levels with moderate or severe disease.<br><br>Moderate disease was defined as fever or other respiratory symptoms as well as bilateral pulmonary lesions confirmed on chest imaging<br>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<br><br>Sample size: 65 (TCZ = 33, Control = 1460)<br><br>Median age = 63.0 years (IQR = 55.0 to 71.0 years). | Participants were randomly assigned in a 1:1 ratio to receive either tocilizumab in addition to standard care, or standard care alone. If a participant in the control group progressed to severe disease within 3 days after randomization, they were transferred to the tocilizumab group. | 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 absorption of chest effusion by more than 50% percent on discharge.<br><br>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).<br><br>For the secondary endpoints of recovery rate of hypoxia over 14 days and the worsening rate of hypoxia during hospitalization:<br><br>Recovery rate of hypoxia:<br>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. | Risk of bias assessment: **HIGH**, as there were concerns regarding the allocation concealment during randomisation.<br>ITT analysis, but small study (n=65).<br>Study unblinded and possible bias with the measurement of the outcome in particular the measurement of adverse events and serious adverse events.<br>Possible bias regarding selection of the reported results, as adverse events were not mentioned in the registry but reported in the paper.<br>The protocol and statistical plans were not available. |
| Published non-peer reviewed<br><br>Rosas I, Bräu N, Waters M, et. al.[23]<br><br>medRxiv 2020<br><br>Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. | Randomized, double-blind, placebo-controlled trial | Setting: 9 Countries - Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK and USA.<br><br>Participants: Patients with PCR confirmed COVID-19 and evidenced by bilateral chest infiltrates on chest x-ray or CT. Participants were also required to have blood oxygen saturation ≤93% or partial pressure of | Participants 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.<br><br>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:<br>TCZ = 1.0 (1.0 to 1.0) for tocilizumab | Risk of bias assessment: **LOW** as blinded study with random allocation sequence and adequate concealment.<br>452/438 patients analysed (>95% of population), and outcomes reported were pre-specified in the registry. |

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| DOI 10.1101/2020.08.27.20183442<br><br>NCT04320615 | | oxygen/fraction of inspired oxygen <300 mmHg.<br><br>Sample size: 438 (TCZ = 294, Control = 144)<br><br>Median age = 63.0 years (IQR = 55.0 to 71.0 years). | | Placebo 2.0 (1.0 to 4.0) (odds ratio, 1.19 [0.81 to 1.76]).<br><br>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).<br><br>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]).<br>Median duration of ICU stay was 5.8 days shorter with tocilizumab than placebo (9.8 and 15.5, respectively; nominal P=0.045). | |
| Published, peer-reviewed<br><br>Veiga VC, Prats JAGG, Farias DLC et. al.[31]<br><br>BMJ 2021<br><br>Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial.<br><br>DOI: 10.1136/bmj.n84<br><br>NCT04403685 | Randomised, open-labelled trial<br><br>08 May to 17 July 2020. | Setting: , 9 hospitals<br><br>Participants: Adult patients with severe PCR-confirmed SARS-CoV-2 infection. Patients were required to have experience symptoms for more than 3 days and present with evidence of pulmonary infiltrates confirmed by chest CT or radiography and were receiving supplemental oxygen or had been receiving mechanical ventilation for less than 24 hours before analysis.<br><br>Sample size: 129 (TCZ = 65, SOC = 64)<br><br>Mean age: | Patients were randomised (1:1) to receive either TCZ (single intravenous infusion of 8 mg/kg) plus standard care or standard care alone.<br><br>Standard of care allowed for the concomitant use of hydroxychloroquine, azithromycin, corticosteroids, and antibiotics as per local institutional guidelines for patients with covid-19. Remdesivir was not available in Brazil at the time of the study. | Primary outcome: clinical status at 15 days evaluated on a seven-level ordinal scale.<br><br>The trial was prematurely after the first interim analysis owing to an excess number of deaths at 15 days in the tocilizumab group<br><br>TCZ was not associated with an improvement in mechanical ventilation or death at 15 days (18 of 65 (28%) patients in the TCZ group and 13 of 64 (20%) in the SOC group: odds ratio 1.54, 95% CI 0.66 - 3.66; P=0.32). Death at 15 days, a component of the primary outcome, occurred in 11 (17%) patients in the TCZ group compared with two (3%) in the SOC group (odds ratio 6.42, 1.59 - 43.2). | Risk of bias assessment: **MODERATE** as study was unblinded study and the outcomes could have been influenced by the intervention assignment. |

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| | | TCZ = 57.4 years (SD = 15.7 years)<br>SOC = 57.5 years (SD = 13.5years) | | | |
| Published, peer reviewed<br><br>Horby PW, Pessoa-Amorim G, Peto L et al. for the RECOVERY Collaborative Group[32]<br><br>Lancet 2021<br><br>Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial<br><br>DOI: 10.1016/S0140-6736(21)00676-0<br><br>NCT04381936, ISRCTN50189673 | Randomised, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]<br><br>23 April 2020 and 24 January 2021 | Setting: United Kingdom, 131 sites<br><br>Participants: Adult hospitalized patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection as well as hypoxia (defined as Sp02 of <92% and a CRP level of ≥75 mg/L).<br><br>Sample size: 4 116 (TCZ = 2 022, SOC = 2 094)<br><br>At the time of this publication, follow-up was completed for 1602 (79%) of the 2022 TCZ patients and 1664 (79%) of the 2094 patients SOC<br><br>Mean age: 63.6 years (SD 13.7) | Patients were randomised (1:1) to receive either TCZ plus standard care or standard care alone. TCZ doses were weight-based (800mg if weight >90kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8mg/kg if weight ≤40 kg). A second dose could be given 12 to 24 hours later if, at the discretion of the attending clinician, the patient's condition had not improved.<br><br>Standard of care is not described.<br><br>At randomisation, 562 (14%) patients were receiving invasive mechanical ventilation, 1686 (41%) were receiving non-invasive respiratory support (including high-flow nasal oxygen, CPAP, and non-invasive ventilation), and 1868 (45%) were receiving no respiratory support other than simple oxygen therapy. | Primary outcome: all-cause mortality at 28 days.<br><br>Secondary outcomes were time to discharge alive from hospital, and, among patients not receiving invasive mechanical ventilation at randomisation, receipt of invasive mechanical ventilation (including extra-corporeal membrane oxygenation) or death.<br><br>TCZ was associated with a 4% absolute reduction 28-day mortality compared with SOC alone (621 [31%] of 2022 patients in the tocilizumab group vs. 729 (35%) of 2094 patients in the usual care group; rate ratio 0.85; 95% confidence interval [CI], 0.76 to 0.94; p=0·0028).<br><br>TCZ was associated with a greater probability of discharge from hospital alive within 28 days (57% vs. 50%; rate ratio 1.22, 95% CI 1.12 to 1.33, p<0·0001). Among those not on invasive mechanical ventilation at baseline, TCZ reduced in the risk of progressing to the pre-specified composite secondary outcome of invasive mechanical ventilation or death when compared to SOC (35% vs. 42%, risk ratio 0.84, 95% CI 0.77 to 0.92, p=0·0001). | Risk of bias assessment: MODERATE as study was unblinded and there were some concerns with the measurement of the outcome: Clinical improvement (D28), defined as discharge from hospital. Assessment requires clinical judgement and could be affected by knowledge of intervention receipt. |
| Published, peer reviewed | Randomised, controlled, open-label phase 3 study | Setting: India, 12 sites | Patients were randomised (1:1) to receive either TCZ plus standard care | Primary outcome: Proportion of patients with progression of | Risk of bias assessment: MODERATE as study was |

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| Soin AS, Kumar K, Choudhary NS, et. al.[33]<br><br>*Lancet Respir Med 2021*<br><br>Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19- associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial<br><br>https://doi.org/10.1016/S2213-2600(21)00081-3<br><br>CTRI/2020/05/025369 | 30 May 2020 and 31 August 2020 | Participants: Hospitalised patients aged 18 years or older with confirmed SARS-CoV-2 infection and moderate to severe disease (**moderate** defined as respiratory rate 15–30 per min [revised to 24 per min on June 13, 2020] and blood oxygen saturation [SpO2] 90–94%; **Severe** defined as respiratory rate ≥30 per min or SpO2 <90% in ambient air, or ARDS or septic shock)<br><br>Sample size: 180 (TCZ = 91, SOC = 88)<br><br>Median age: TCZ = 56 years range 47 - 63); SOC = 54 years (range 43-63) | or standard care alone. TCZ was administered as a single IV infusion at 6mg/kg up to a maximum dose of 480mg. An additional dose of 6mg/kg (max 480mg) could be administered if clinical symptoms worsened or did not show improvement within 12 hours to 7 days after the first dose.<br><br>The dosing regimen was selected on the basis of the cost and supply considerations in India and because a single dose between 4 mg/kg and 8 mg/kg plus an additional dose to a maximum of 800 mg, if required, had been recommended on the basis of initial reports on the use of tocilizumab in the treatment of COVID-19 in China.<br><br>Standard of care included corticosteroids equivalent to methylprednisolone 1 mg/kg or less if deemed necessary by the treating physician. Supplemental oxygen was recommended to treat hypoxia, and high-flow nasal cannula, non-invasive ventilation, and mechanical ventilation could be considered if hypoxia and respiratory distress progressed. | COVID-19 from moderate to severe or from severe to death up to day 14.<br><br>The proportion of patients with progressive COVID-19 up to day 14 was 9% (eight of 91) in the TCZ group and 13% (11 of 88) in the SOC group. The difference was not statistically significant (–3.71 [95% CI –18.23 to 11.19]; p=0.42). | unblinded and there were some concerns with the measurement of the outcomes of mortality (D28), adverse events and serious<br><br>adverse events. |
| Published, non-peer reviewed<br><br>Talaschian M, Akhtari M, Mahmoudi M, et. al. 34<br><br>*Research Square 2021*<br><br>Tocilizumab failed to reduce mortality in severe COVID-19 patients: Results from a randomized controlled clinical trial. | Randomised, controlled, double-blind, two-arm parallel, phase 2 study<br><br>10 July 2020 and 10 October 2020 | Setting: Tehran, Iran. Single site<br><br>Participants: Non-ventilated patients, hospitalised adult patients (18 years and older) with confirmed SARS-CoV-2 infection (via positive PCR result and atypical CT features) not responding to standard COVID-19 treatment and have: | Patients were randomised (1:1) to receive either TCZ plus standard care or standard care alone. TCZ dose of 8mg/kg to a maximum of 800mg was administered to the TCZ group within 2 days of hospitalization. A second dose could be given 12 hours later if, the patient's condition was not stable. | Primary outcome: mortality at 28 days.<br><br>Death was reported in 29.4% of the TCZ arm and 21.1% of the SOC arm. This difference was not statistically significant. [Log rank test: P=0.973; Hazard ratio: 1.25; 95% CI: 0.249-4.209]. | Small study (n=40) using an intention to treat analysis.<br><br>Overall risk of bias assessment: **HIGH**<br>• *Randomisation:* Allocation sequence probably random (block randomisation), but unclear allocation concealment – **MODERATE RISK.**<br>• *Deviations from intervention:* "In this study, patients, investigators, and outcome assessors did not inform which group received an |

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| https://doi.org/10.21203/rs.3.rs-463921/v1<br><br>IRCT20081027001411N4 | | 1. CRP levels of ≥10 mg/L, or IL-6 of 18pg/ml or lymphopenia (<1100/MCL), and<br>2. Sp02 <93% or respiratory rate higher than 24.<br><br>Sample size: 40 patients (TCZ = 20, SOC = 20)<br><br>Mean age = 61.74 ± 14.19 years old | | | intervention. Besides, a placebo was not used in the control group". Unclear blinding and antivirals not distributed between intervention (TCZ) and standard of care group (35% vs 10%) – **MODERATE RISK.**<br>• *Missing outcome data:* 40 participants randomized; 36 participants analyzed. 3 participants in the treatment arm and 1 in the standard care arm refused to participate before start of the intervention – **MODERATE RISK.**<br>• *Measurement of the outcome:* Outcome assessors were blinded – **LOW RISK.**<br>• *Selection of the reported results:* Trial probably not analyzed as prespecified. Mortality outcome has different time point listed in the registry compared to the report. Neither are the outcomes of clinical improvement and serious adverse events not prespecified — **MODERATE RISK.** |
| Published, non-peer reviewed<br><br>Rutgers M, Westerweel PE, van der Holt B, et.al.[35]<br><br>*SSRN 2021*<br><br>Timely administration of tocilizumab improves survival of hospitalized COVID-19 patients.<br><br>http://dx.doi.org/10.2139/ssrn.3834311 | Prospective, randomised, controlled, phase 2 study<br><br>06 April 2020 and 12 January 2021 | Setting: Netherlands, 11 sites<br><br>Participants: Hospitalised adult patients (18 years and older) with confirmed SARS-CoV-2 infection (via positive PCR result and have signs compatible with hyper inflammation, namely a need for supplemental oxygen (SpO2 < 94% and/or ferritin >2000ug/l or a doubling of serum ferritin in 20-48 hours<br><br>Sample size: 354 patients (TCZ = 174, SOC = 180) | Patients were randomised (1:1) to receive either TCZ plus standard care or standard care alone. TCZ dose of 8mg/kg to a maximum of 800mg was administered to the TCZ group within 2 days of hospitalization. A second dose could be given after 8 hours if hypoxia was not resolved.<br><br>88% of patients received dexamethasone as concomitant treatment. Remdesivir and hydroxychloroquine were both allowed as concomitant therapies. | Primary outcome: mortality at 30 days.<br><br>Death was reported in 29.4% of the TCZ arm and 21.1% of the SOC arm. This difference was not statistically significant. [Log rank test: P=0.973; Hazard ratio: 1.25; 95% CI: 0.249-4.209].<br><br>For secondary outcomes measures, there was no difference in duration of hospital stay, percentage of patients admitted to ICU, number of patients ventilated or duration of ventilation. However, the | Overall risk of bias assessment: **MODERATE.** Concerns were noted with the randomization of the patient population. |

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| Trial NL8504 | | Mean age = 66 years (range 56 - 75 years); SOC = 67 years (60 - 74 years) | | median duration of ICU stay was significantly shorter in patients receiving TCZ (9 days, IQR 5-16 days vs. 16 days, IQR 8-30 p=0.025). | |

## Appendix 1: GUIDELINE CONSIDERATIONS

### 1. NIH COVID-19 Treatment Guidelines (updated 21 April 2021)[17]

*Interleukin-6 Inhibitors*

**Recommendations:**

- The Panel recommends using tocilizumab (single intravenous [IV] dose of tocilizumab 8 mg/kg actual body weight up to 800 mg) in combination with dexamethasone (6 mg daily for up to 10 days) in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19. These patients are:
  - Recently hospitalized patients (i.e., within first 3 days of admission) who have been admitted to the intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow nasal canula (HFNC) oxygen (>0.4 FiO2/30 L/min of oxygen flow) (BIIa); or
  - Recently hospitalized patients (i.e., within first 3 days of admission) not admitted to the ICU who have rapidly increasing oxygen needs and require noninvasive ventilation or HFNC oxygen and who have significantly increased markers of inflammation (CRP ≥75 mg/L) (BIIa).
- For hospitalized patients with hypoxemia who require conventional oxygen therapy, there is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Some Panel members would also give tocilizumab to patients who are exhibiting rapidly increasing oxygen needs while on dexamethasone and have a CRP ≥75 mg/L, but who do not yet require noninvasive ventilation or HFNC oxygen as described above.
- There are insufficient data for the Panel to recommend either for or against the use of sarilumab for hospitalized patients with COVID-19 who are within 24 hours of admission to the ICU and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow oxygen (>0.4 FiO2/30 L/min of oxygen flow).
- The Panel **recommends against** the use of anti-IL-6 monoclonal antibody therapy (i.e., siltuximab) for the treatment of COVID-19, except in a clinical trial (BI).

### 2. World Health Organization: COVID-19 Clinical management: living guidance, 25 January 2021[18]:

It is noted that no guidance has been provided for the use of IL-6 inhibitors in the WHO Therapeutics and COVID-19 living guideline of 31 March 2021.

### 3. Australian guidelines for the clinical care of people with COVID-19. Version 34.1 (updated 13 May 2021)[27]

*6.3.1 Tocilizumab*

**Recommendation:** Consider using tocilizumab for the treatment of COVID-19 in adults who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes, with the potential for a second dose to be administered either 12 or 24 hours later if the patient's condition has not improved. The suggested dose is dependent on body weight:

- Patients > 90 kg: 800 mg tocilizumab
- Patients > 65 and ≤ 90 kg: 600 mg tocilizumab
- Patients > 40 and ≤ 65 kg: 400 mg tocilizumab
- Patients ≤ 40 kg: 8 mg/kg tocilizumab

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab. Use of combined tocilizumab and corticosteroids should be considered in patients hospitalised with COVID-19 who require oxygen, however the optimal sequencing of tocilizumab and corticosteroid use is unclear.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

## 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.

**Search Strategy 3:**
*Date:* 13 January 2021

**Epistemonikos L*OVE evidence platform:**

Tocilizumab

**Records retrieved:** Randomised controlled trials and systematic reviewed published in December 2020 and January 2021. Three RCTs were eligible, however only one pertained to data not previously reviewed and thus was included in this update. No systematic reviews were found published after 15 November 2020 that included the randomized controlled trial described above.

**Search Strategy 4:**

*Date:* 18 May 2021

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

Tocilizumab

**Records retrieved: 12 RCTs**

## Appendix 3: Forest plots for Cochrane Living Meta-analysis: Tocilizumab compared to Standard of care/Placebo for Mild/Moderate/Severe/Critical COVID-19

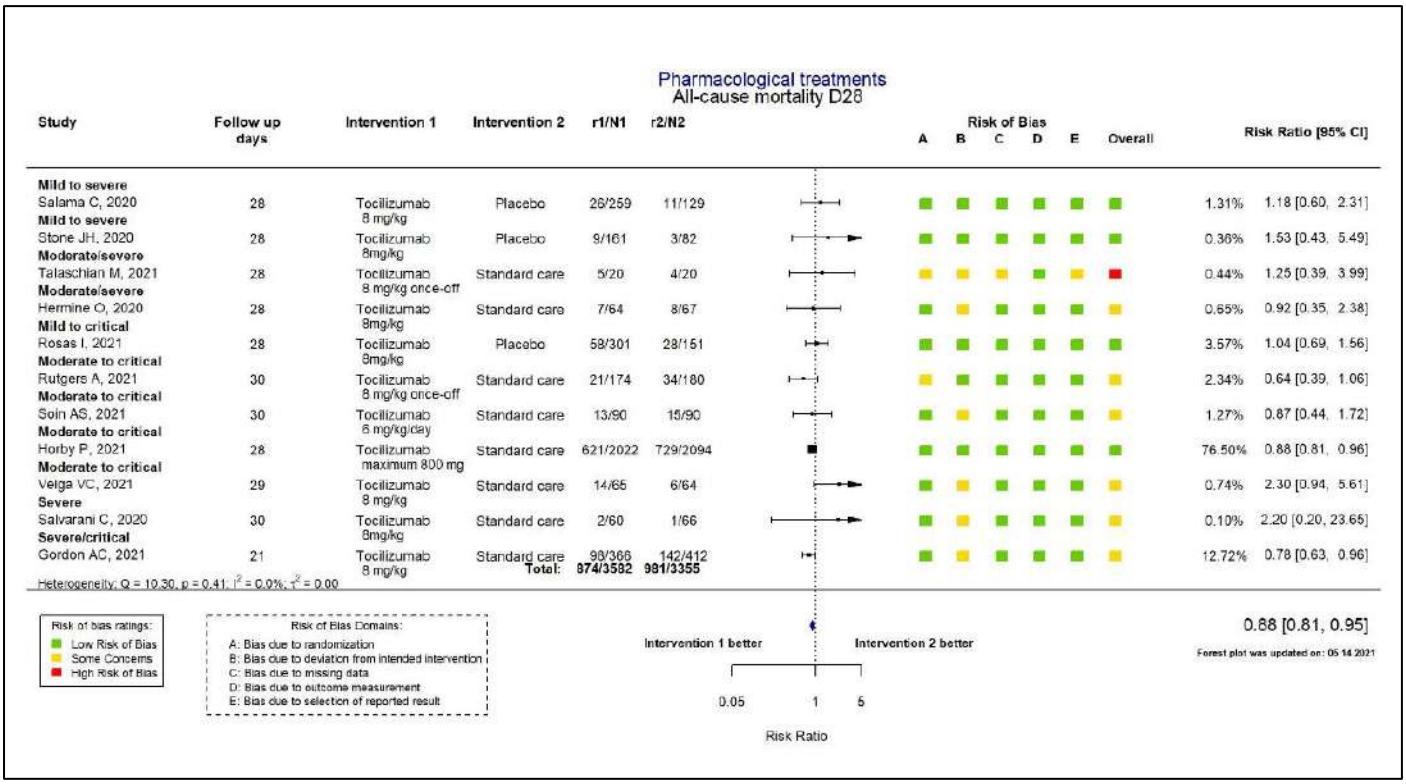


**Figure 1:** All-cause mortality, D28: Tocilizumab compared to Standard of care/Placebo

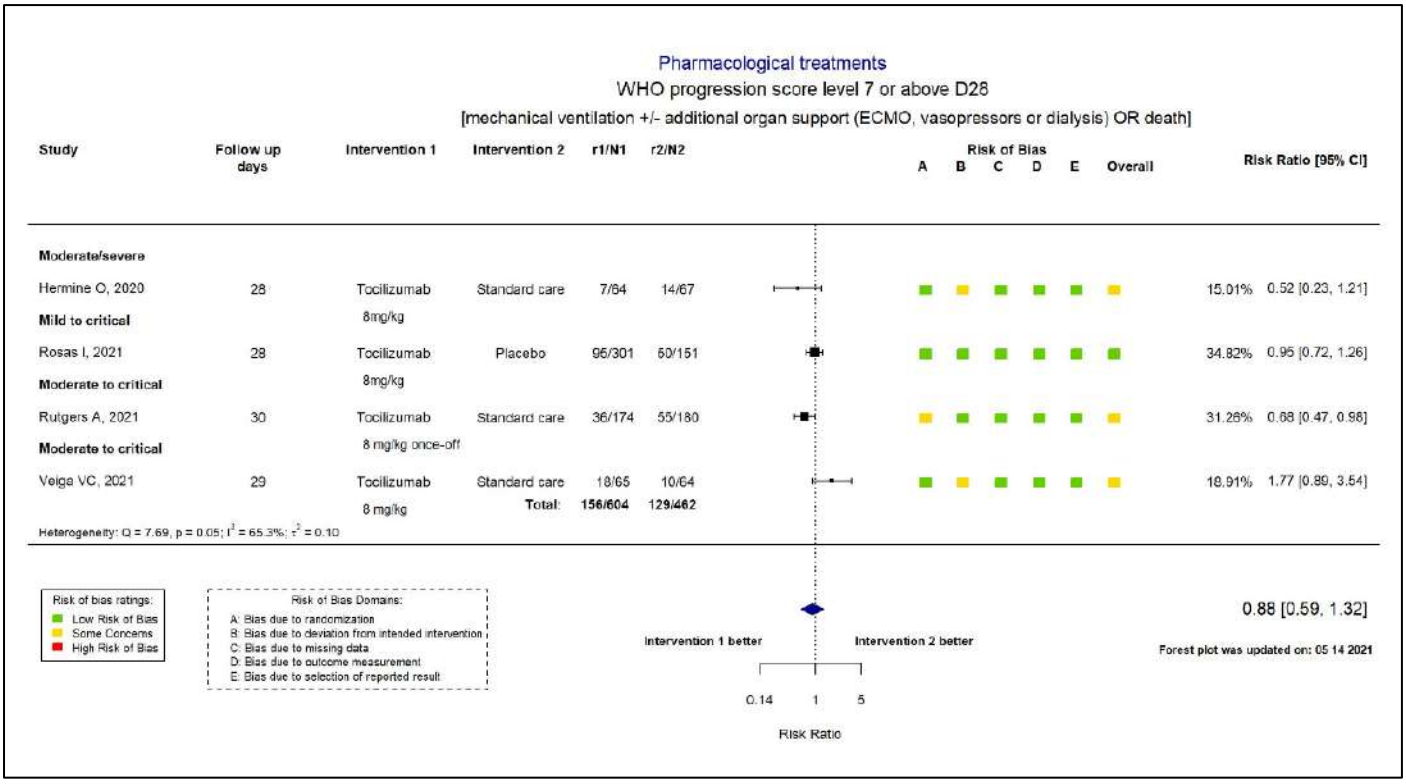


**Figure 2:** WHO progression score level 7 or above at Day 28 [mechanical ventilation ± additional organ support (ECMO, vasopressors or dialysis) OR death.

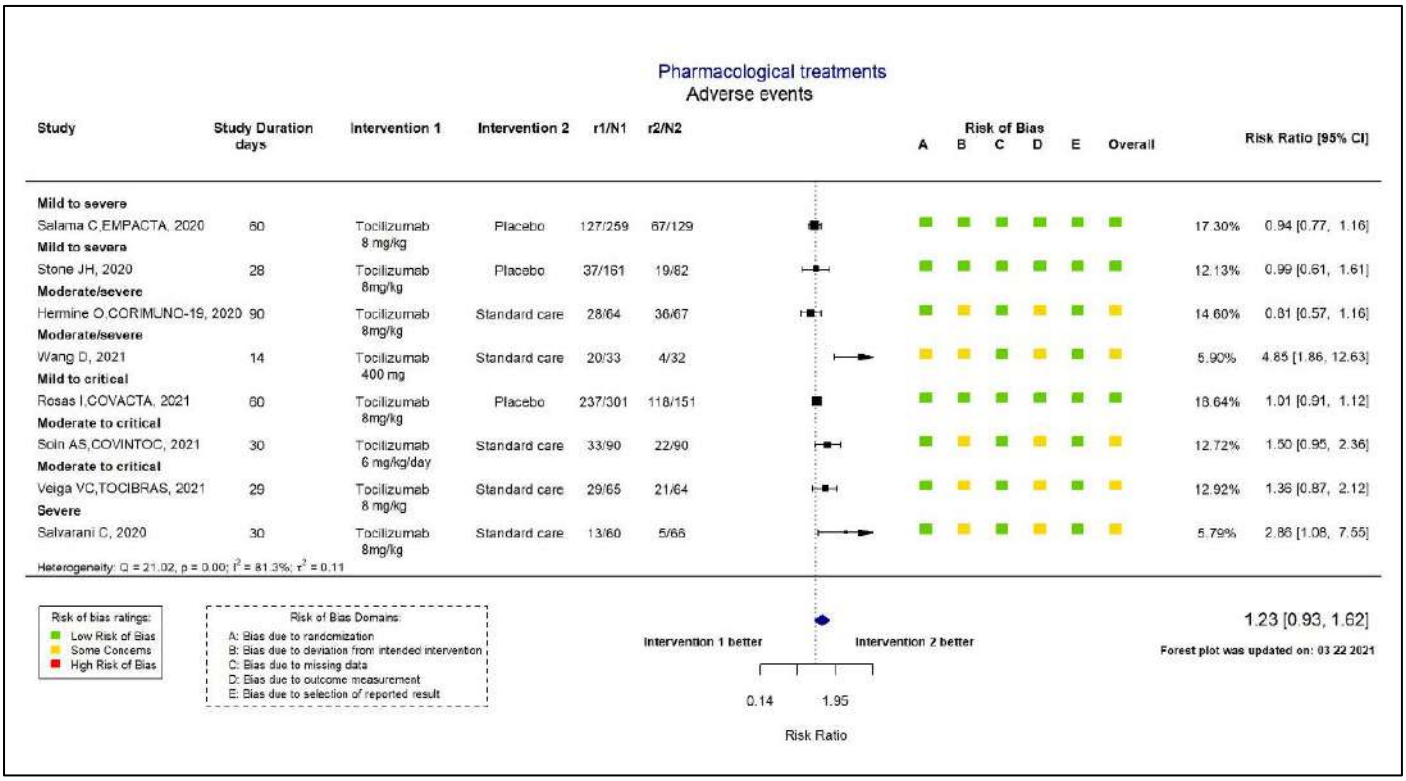


**Figure 3:** Adverse events: Tocilizumab compared to Standard of care/placebo

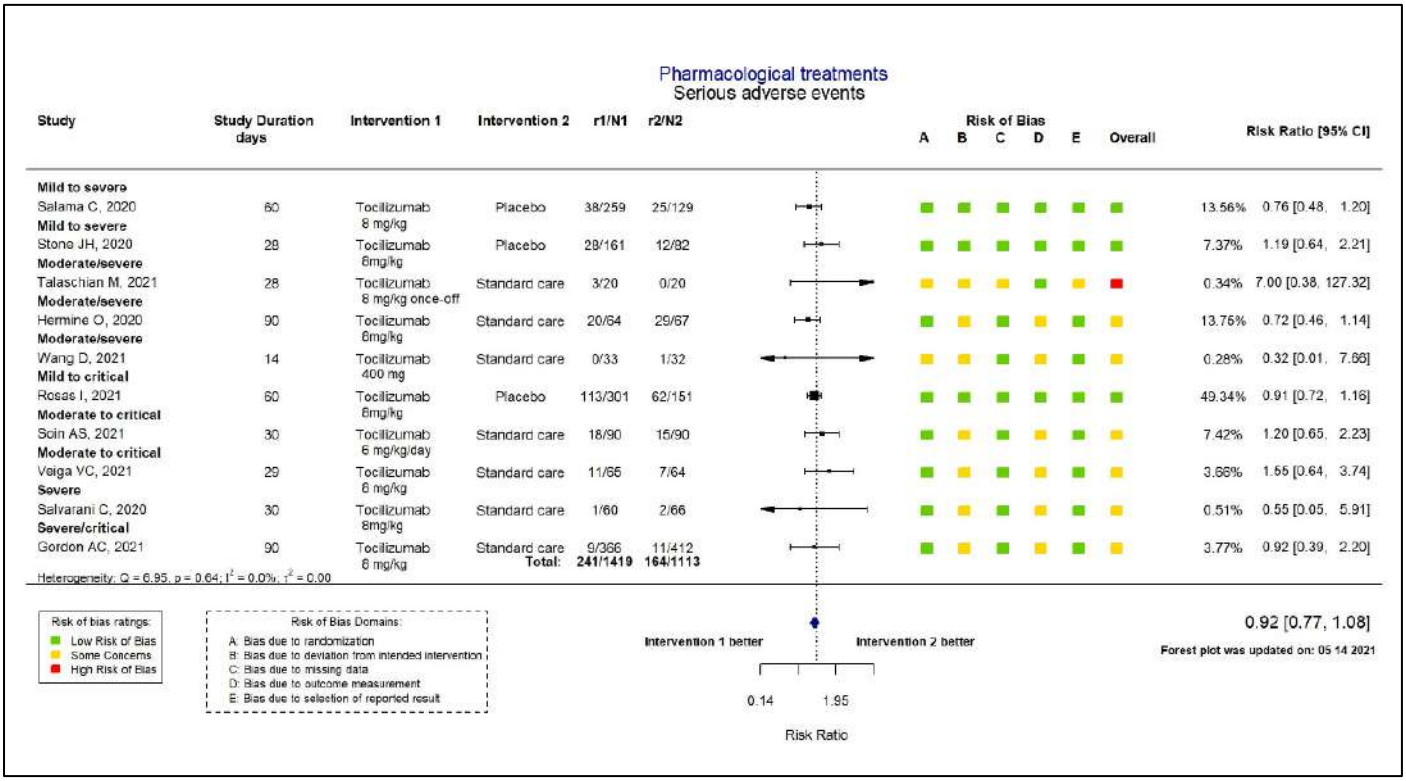


**Figure 4:** Serious adverse events: Tocilizumab compared to Standard of care/Placebo

## Appendix 4: Evidence to decision framework

| | JUDGEMENT | EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| **EVIDENCE OF BENEFIT** | **What is the size of the effect for beneficial outcomes?**<br>Large ☐ Moderate ☒ Small ☐ None ☐ Uncertain ☐ | A meta-analysis of 12 RCTs demonstrated that TCZ is associated with an all-cause mortality benefit at 28 days. ARR 3.5% (95% CI 1.5% to 5.6%); RR 0.88 (95% CI 0.81 to 0.85, eleven RCTs, n = 6 937). NNT 29 (95% CI 18 to 67) to prevent 1 death. |
| **EVIDENCE OF HARMS** | **What is the size of the effect for harmful outcomes?**<br>Large ☐ Moderate ☐ Small ☐ None ☒ Uncertain ☐ | No increased risk of infections or adverse events was observed with tocilizumab use in the RCTs [29] |
| **BENEFITS & HARMS** | **Do the desirable effects outweigh the undesirable harms?**<br>Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐ | Available evidence shows that TCZ is associated with an all-cause mortality benefit at 28 days, with no reports of associated increased risk of infections or adverse events. |
| **QUALITY OF EVIDENCE** | **What is the certainty/quality of evidence?**<br>High ☒ Moderate ☐ Low ☐ Very low ☐<br>*High quality:* confident in the evidence<br>*Moderate quality:* mostly confident, but further research may change the effect<br>*Low quality:* some confidence, further research likely to change the effect<br>*Very low quality:* findings indicate uncertain effect | The findings are based on the finding of a large RCT and meta-analysis of 12 RCTs.<br><br>Assessed per outcome – refer to table 1:<br>• Mortality at D28: high certainty evidence.<br>• WHO progression score (level 7 or above) D28: low certainty evidence<br>• Serious adverse events: moderate certainty evidence |
| **FEASABILITY** | **Is implementation of this recommendation feasible?**<br>Yes ☐ No ☐ Uncertain ☒ | Tocilizumab is SAHPRA registered and available on the South African market, however price and affordability is a concern. |
| **RESOURCE USE** | **How large are the resource requirements?**<br>More intensive ☒ Less intensive ☐ Uncertain ☐ | **Price of medicines/dose** (8mg/kg)<br>**Medicine** / **Offered price***<br>60 kg patient: Tocilizumab 480mg — R 4 435.64<br>75 kg patient: Tocilizumab 600mg — R 5 253.92<br>Maximum dose: Tocilizumab 800mg — R 7 005.16<br>***Offered price from Roche Products (Pty) Ltd (letter dated 30 March 2021)**<br>400mg/20ml = R 3 502.58; 200mg/10ml = R 1 751.34; 80mg/4ml = R 933.06<br><br>**Basic costing analysis:**<br>• *Clinical inputs:*<br>*- Public sector hospitalizations in 1st and 2nd waves:* ≈ **40000 and 60000, respectively (DATCOV survey)**<br>*(Note: Number of public facilities reporting data improved in the second wave; and modelling data for 3rd wave predictions was not available from South African COVID-19 Modelling Consortium, at the time of this report)*<br><br>*- Incidence of elevated CRP>75 mg/l:* **30-50%** (Western Cape PHDC)<br>○ >75 mg/l = 7867/26351 = 30%<br>○ >150 mg/l = 4528/26351 = 20%<br><br>• *Assumptions:*<br>- DATCOV hospital surveillance data assumed to project total future national COVID-19 hospitalizations. Average for 3rd wave 50000 (lower and upper limit of 40000 and 60000, respectively).<br>*Note: Timing of the effect of COVID-19 vaccine on herd immunity needs consideration* |

| | | |
|---|---|---|
| | | - Western Cape data regarding the incidence of raised CRP assumed to be generalisable to the whole country. Average of 40% (upper and lower limit of 30% and 50%, respectively).<br>- Patient with CRP>75mg/l assumed to be severe, requiring supplemental oxygen.<br><br>• *Estimated forecast:*<br>- Estimated number of patients who will be eligible for tocilizumab treatment: 20000 (lower and upper limit of 12000 and 30000, respectively).<br><br>• *Estimated budget impact at current SEP:*<br>- Treatment cost (using offered price of 30 March 2021) @R5 250 per patient (75 kg); then total cost estimated as R105 mil (lower and upper limit of R65 mil to R160 mil).<br><br>• *References*<br>- Data on file, Western Cape NHLS<br>- Data on file, DATCOV reports, NICD<br>- Offered price from Roche Products (Pty) Ltd (letter dated 30 March 2021)<br>- Rapid review of Tocilizumab for CoVID-19 Update, 3 March 2021 |
| **VALUES, PREFERENCES, ACCEPTABILITY** | **Is there important uncertainty or variability about how much people value the options?**<br>Minor [ ] Major [ ] Uncertain [X]<br><br>**Is the option acceptable to key stakeholders?**<br>Yes [X] No [ ] Uncertain [ ] | No specific research surveying patients' or healthcare workers' value of this therapeutic agent is currently available.<br><br>The Committee was of the opinion that the option would be acceptable to key stakeholders. |
| **EQUITY** | **Would there be an impact on health inequity?**<br>Yes [ ] No [ ] Uncertain [X] | Tocilizumab currently only available in private sector and is expensive. |

## Appendix 5: Updating of rapid report

| Date | Signal | Rationale |
|---|---|---|
| 10 January 2021 & 11 February 2021 | Preprints of REMAP-CAP and RECOVERY trials | The preliminary study results of the tocilizumab arm of the REMAP-CAP and RECOVERY trials have been published in preprint format |
| 6 May 2021 | RECOVERY trial published in Lancet | The RECOVERY trial data is now published in peer review format. |
| 25 February 2022 | Motivation from KwaZulu-Natal Pharmaceutics and Therapeutics Committee | Approved immunomodulatory, baricitinib cannot be used in pregnancy. Consideration for tocilizumab-use for this patient cohort. |

## ADDENDUM A

### MANAGEMENT OF SEVERE COVID-19 IN PREGNANCY: TOCILIZUMAB AND BARICITINIB

**Date:** 6 April 2022 (Addendum to baricitinib and tocilizumab rapid reviews)

## Background

COVID-19 during pregnancy is associated with an increased risk of adverse maternal and neonatal outcomes.[1]

Previously, the NEML MAC on COVID-19 Therapeutics issued a conditional recommendation in support of baricitinib in hospitalised patients with confirmed COVID-19 who required oxygen and had at least one raised inflammatory marker.[2] Although the recommendation did not specifically consider the suitability of baricitinib in pregnant women, the current professional information (PI) is explicit that baricitinib is contraindicated in pregnancy.[3] The PI states that "The JAK/STAT[a] pathway is involved in cell adhesion and cell polarity which can affect early embryonic development. Animal studies have associated baricitinib with reproductive toxicity as well as adverse effects on *in utero* bone development at higher dosages. Furthermore, baricitinib was teratogenic in rats and rabbits." Therefore, although the MAC recommended baricitinib in the management of severe COVID-19 because of mortality benefit, baricitinib is contraindicated in pregnant women with severe COVID-19 because of serious concerns of foetal harm.

Tocilizumab is an alternative immunomodulator that could potentially be used in combination with corticosteroids in this patient group. Tocilizumab was reviewed by the NEML MAC on COVID-19 Therapeutics in May 2021[4] and a conditional recommendation not to use tocilizumab was made, in view of the unaffordable price and concerns about supply constraints. This addendum has been produced in response to a request for guidance on the use of tocilizumab, specifically in the management of pregnant women with severe COVID-19, where baricitinib cannot not be used.

## Method

On 06 April 2022, both PubMed and the Epistemonikos L*OVE evidence platform (https://app.iloveevidence.com/) were searched for publications relevant to this subgroup of patients. The search strategy is represented in Appendix 1.

## Results

We did not find any randomized controlled trials investigating the use of TCZ in pregnant women with COVID-19. Data that were available was limited to observational studies in small numbers of patients. The bulk of data on use of TCZ pregnancy comes from patients treated for rheumatological conditions.

We identified a 2021 narrative review which included observational data from 610 TCZ-exposed pregnancies, of which 20 were pregnant women with COVID-19.[5] The authors did not identify any serious safety signals, but concluded that there were insufficient data available to adequately characterize the safety of TCZ in pregnancy. Most TCZ exposures in this review were during the first trimester, with very little data on TCZ exposure in the second and third trimesters, when transplacental transfer of TCZ is likely to be higher than in the first trimester. The effects of TCZ on development of the foetal immune system are not known. The bulk of the data included in the narrative review comes from Roche's Global safety database (180 prospective and 108 retrospective reports) and the European League against Rheumatism (EULAR) taskforce reports (218 reports derived from registration data and conference abstracts). Both of these studies found that rates of prematurity were higher than in the general population (31% vs 10-15%), and there was a lower mean birthweight which was only partially explained by gestational age. The extent to which the underlying rheumatological condition and/or other concomitant medicines contributed to these findings is not clear. All of the 17 patients from the Roche Global database with TCZ exposure after the first trimester gave birth to live neonates; half were preterm deliveries.

[a] *Janus kinase-signal transducer and activator of transcription*

## Conclusion

Although no randomized controlled trial data was found to support the safe and effective use of TCZ in pregnant women with severe COVID-19, there is no evidence to suggest these patients would respond differently when compared with other adults.[6] No serious safety signals have been identified to date, but data are limited. The number of TCZ-exposed pregnancies was small, and most exposures were in the first trimester. TCZ may be associated with increased rates of premature deliver, but it is not clear to what extent underlying rheumatological disorders and/or concomitant medicines contributed to this finding .[5]

Although the use of tocilizumab in pregnant women with severe COVID-19 is not recommended, clinicians should assess the individual risk-benefit in each case, and can consider the addition of this agent to an appropriate parenteral corticosteroid (such as hydrocortisone).

**Reviewers:** Roger Wiseman (Liberty Health (Pty) Ltd, South Africa), Marc Blockman (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town) have no interests pertaining to tocilizumab.

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## Appendix 1 (Addendum A): Search strategy

Date: 06 April 2022

**PubMed**

(("tocilizumab"[Supplementary Concept] OR "tocilizumab"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields])) AND (humans[Filter])

**Records retrieved:** 21 (0 RCTs or systematic reviews, 3 case studies, 1 narrative review)

**Epistemonikos L*OVE evidence platform:**

Tocilizumab for pregnant women

**Records retrieved:** 17 (0 RCTs or systematic reviews, 2 case reports, 1 retrospective review).

## Appendix 2 (Addendum A): GUIDELINE CONSIDERATIONS

### 4. Australian guidelines for the clinical care of people with COVID-19. Version 53.1 (updated 08 March 2022)[7]

*6.1.6.3.2 Tocilizumab for pregnant or breastfeeding women*

**Conditional recommendation:** Consider using tocilizumab for the treatment of COVID-19 in pregnant or breastfeeding women who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes. The suggested dose is dependent on body weight:

- Patients > 90 kg: 800 mg tocilizumab
- Patients 66–90 kg: 600 mg tocilizumab
- Patients 41–65 kg: 400 mg tocilizumab
- Patients ≤ 40 kg: 8 mg/kg tocilizumab

In pregnant and breastfeeding women, dosing should be based on body weight at time of clinical need.
In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

For the babies of women who received tocilizumab during pregnancy (after 20 weeks of gestation), live vaccines (rotavirus and BCG) should be avoided in the first six months of life. All non-live vaccinations are safe and should be undertaken (see factsheet).

In women who receive tocilizumab while breastfeeding only, live vaccines (rotavirus and BCG) can be given to the baby (see factsheet).

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab. Use of combined tocilizumab and corticosteroids should be considered in patients hospitalised with COVID-19 who require oxygen, however the optimal sequencing of tocilizumab and corticosteroid use is unclear.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

# DRUG TREATMENTS FOR PREGNANT OR BREASTFEEDING WOMEN WITH COVID-19

| DEFINITION OF DISEASE SEVERITY | Not requiring oxygen WITHOUT lower respiratory tract disease | Not requiring oxygen WITH lower respiratory tract disease | Requiring oxygen WITHOUT mechanical ventilation | Requiring invasive mechanical ventilation |
|---|---|---|---|---|
| | **Mild**<br>An individual with no clinical features suggestive of moderate or more severe disease:<br>• no OR mild symptoms and signs (fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell)<br>• no new shortness of breath or difficulty breathing on exertion<br>• no evidence of lower respiratory tract disease during clinical assessment or on imaging (if performed) | **Moderate**<br>A stable patient with evidence of lower respiratory tract disease:<br>• during clinical assessment, such as<br>– oxygen saturation 92-94% on room air at rest<br>– desaturation or breathlessness with mild exertion<br>• or on imaging | **Severe**<br>A patient with signs of moderate disease who is deteriorating<br>OR<br>A patient meeting any of the following criteria:<br>• respiratory rate ≥30 breaths/min<br>• oxygen saturation <92% on room air at rest or requiring oxygen<br>• lung infiltrates >50% | **Critical**<br>A patient meeting any of the following criteria:<br>• respiratory failure (defined as any of)<br>– severe respiratory failure ($PaO_2/FiO_2$ <200)<br>- respiratory distress or acute respiratory distress syndrome (ARDS)<br>– deteriorating despite non-invasive forms of respiratory support (i.e. non-invasive ventilation (NIV), or high-flow nasal oxygen (HFNO))<br>– requiring mechanical ventilation<br>• hypotension or shock<br>• impairment of consciousness<br>• other organ failure |
| **RECOMMENDED** | | | Use **dexamethasone** intravenously or orally for up to 10 days in pregnant or breastfeeding women with COVID-19 who ***require oxygen*** (including mechanically ventilated patients).<br>If steroids are indicated for fetal lung maturity in women at risk of preterm birth, a standard antenatal corticosteroid regimen should be used.<br>If steroids are not indicated for fetal lung maturity, use dexamethasone daily intravenously or orally for up to 10 days. | |
| **CONDITIONAL RECOMMENDATION** | Consider using inhaled **corticosteroids (budesonide or ciclesonide)** ***within 14 days of symptom onset*** in adults with COVID-19 who ***do not require oxygen*** and have one or more ***risk factors***^ for disease progression. | | **Consider using one of the following:**<br>Consider using **tocilizumab** for the treatment of COVID-19 in pregnant or breastfeeding women who ***require supplemental oxygen***, particularly where there is evidence of ***systemic inflammation.*** | |
| **CONDITIONAL RECOMMENDATION AGAINST** | **DO NOT** routinely use **dexamethasone** (or other systemic corticosteroid) to treat COVID-19 in pregnant or breastfeeding women who ***do not require oxygen***. | | | |
| **NOT RECOMMENDED** | **DO NOT** use the following for the treatment of COVID-19:<br>• aspirin<br>• azithromycin<br>• colchicine<br>• convalescent plasma<br>• hydroxychloroquine<br>• hydroxychloroquine plus azithromycin<br>• interferon β-1a<br>• interferon β-1a plus lopinavir-ritonavir<br>• ivermectin<br>• lopinavir-ritonavir | | | |
| | | | **DO NOT** start **remdesivir** in pregnant or breastfeeding women hospitalised with COVID-19 who ***require non-invasive or invasive ventilation.*** | |
| **ONLY IN RESEARCH** | Do not use the following for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval:<br>• anakinra<br>• angiotensin 2 receptor agonist C21<br>• aprepitant<br>• baloxavir marboxil<br>• bamlanivimab<br>• bamlanivimab plus etesevimab<br>• baricitinib<br>• bromhexine hydrochloride<br>• camostat mesilate<br>• chloroquine<br>• combined metabolic activators (CMA)<br>• darunavir-cobicistat<br>• doxycycline<br>• dutasteride<br>• enisamium<br>• favipiravir<br>• fluvoxamine<br>• human umbilical cord mesenchymal stem cells<br>• immunoglobulin<br>• immunoglobulin plus methylprednisone<br>• inhaled interferon β-1a<br>• interferon β-1b<br>• interferon gamma<br>• interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2)<br>• ivermectin plus doxycycline<br>• lenzilumab<br>• molnupiravir (Lagevrio)<br>• N-acetylcysteine<br>• nirmatrelvir plus ritonavir (Paxlovid)<br>• nitazoxanide<br>• peginterferon lambda<br>• recombinant human granulocyte colony-stimulating factor (rhG-CSF)<br>• regdanvimab<br>• ruxolitinib<br>• sarilumab<br>• sofosbuvir-daclatasvir<br>• sulodexide<br>• telmisartan<br>• tixagevimab plus cilgavimab (Evusheld)<br>• tofacitinib<br>• triazavirin<br>• umifenovir<br>• vitamin C<br>• vitamin D analogues (calcifediol / cholecalciferol)<br>• zinc<br>• other disease-modifying treatments | | | |

Note: This flowchart does not apply to people on home oxygen due to pre-existing conditions. Use clinical judgement in these cases.

The Taskforce recognises that individuals have diverse gender identities. When we use the terms woman, mother or maternity, it is not meant to exclude those who are pregnant or breastfeeding and do not identify as women.

**Source**
**Adapted with permission from National COVID-19 Clinical Evidence Taskforce** – Australian guidelines for the clinical care of people with COVID-19.

Graphic design: Mical Jones mical@morphadezign.co.za