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

TITLE: INTERLEUKIN-6 INHIBITOR, TOCILIZUMAB, FOR COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 15 April 2020

Key findings

- A rapid review was conducted of the available clinical evidence pertaining to the use of tocilizumab with or without other medicines for patients with severe COVID-19 requiring oxygen or ventilatory assistance.
- No systematic reviews, or controlled studies (randomized or other) were found on this topic. Two case series (single arm cohorts) from China were identified and included in this review.
- The included studies did not have any comparator group and all patients received tocilizumab in addition to other clinician-selected medicines that may have activity against SARS-CoV2. Therefore the benefits and harms of tocilizumab, in this clinical setting could not be quantified.
- No reports on the use of tocilizumab in children with COVID-19 were identified and its use in this patient subgroup is discouraged outside of a clinical trial setting.
- There is currently insufficient evidence to support the inclusion of tocilizumab in treatment guidelines for COVID-19 in South Africa until new evidence pertaining to efficacy and safety are published.
- Tocilizumab in the management of severe COVID-19 should only be considered for use within the context of a clinical trial setting.

THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

There is currently insufficient evidence to recommend routine use of tocilizumab in children or adult patients with COVID-19.

Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.

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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 11 April 2020, 15 clinical trials investigating the role of TCZ in the management of COVID-19 are registered on https://clinicaltrials.gov/.

BACKGROUND

The novel human respiratory coronavirus (SARS-CoV-2), which causes COVID-2019, was declared a pandemic by the World Health Organization on 11 March 2020. There are currently more than 1 850 000 confirmed COVID-19 cases in over 200 countries, areas or territories. Moreover, SARs-CoV-2 has caused more than 114 000 deaths (WHO 2020; as at 08h00 13 April, https://coronavirus.jhu.edu/map.html).

In patients infected with SARS-CoV-2, it has been described that 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) has been reported as being 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]. Furthermore, it appears that IL-6 is one of the most important cytokines involved in COVID-19-induced cytokine storms and that 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]

Retrospective case series and individual case reports from China have 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, 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 that TCZ may become an important medicine in the management COVID-19. [14] Notwithstanding, the safety and efficacy of TCZ and other IL-6 inhibitors in the management of COVID-19 has yet to be determined through randomised controlled trials[15]. In the interim, it is necessary to understand the available evidence for the use of IL-6 inhibitors in this indication.

Although there is limited real-life data about the effect of TCZ on the inflammatory activity in COVID-19 patients, this agent has 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]

This review focuses specifically on TCZ as it is the only IL-6 inhibitor commercially available in South Africa.

Note: Due to the continuous emergence of new evidence, this rapid review will be updated as and when more evidence becomes available.

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

We conducted a rapid review of the evidence including 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). Single case reports were excluded. Screening of records and data extraction was conducted by one reviewer, with results reviewed and checked by another reviewer. Relevant records were extracted in a narrative table of results. No appraisal or meta-analysis was done. The search strategy is shown in Appendix 1.

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: Case series, non-randomised cohorts as well as randomised controlled trials, and systematic reviews of studies in humans.

RESULTS

We searched PubMed, as well as the Epistemonikos, Cochrane COVID Study Register and Living Mapping and Living Network meta-analysis of COVID-19 studies electronic databases on 11 April 2020. Details of each search are provided in Appendix 1. One reviewer screened 68 records and identified 2 potentially eligible articles. Data in **Table 1** report the main characteristics and outcomes of the included studies.

There were no randomized controlled trials or systematic reviews/meta-analyses published in this subject area. The included studies were both retrospective case series from China[8, 10]. Neither study included a comparator arm in which tocilizumab was not administered.

Quality appraisal of included studies was not done. However, both studies are observational and neither of them included a comparator arm. Therefore, they do not provide data to adequately inform the assessment of efficacy or safety of TCZ in the treatment of COVID-19.

CONCLUSION

There is currently insufficient evidence to support the use of tocilizumab in the management of COVID-19 in South Africa outside of the clinical trial setting. Eligible patients in South Africa should be considered for enrolment in randomised clinical trials of potential therapies for COVID-19, so that robust data on efficacy and safety of interventions can be generated to inform treatment policies in future.

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

Citation	Study design	Population (n)	Treatment	Main findings
Published, peer reviewed Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J[8] Journal of Medical Virology. 2020 Tocilizumab treatment in COVID-19: a single center experience https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25801	Retrospective case series. Single-centre observational study. 27 January 2020 to 05 March 2020.	Setting: China, 1 medical institution in Wuhan, China Patients: hospitalized patients with COVID-19 who were treated with TCZ. Sample size: 15 (12 males, 3 females) Median age = 73 years (range 62 - 80 years). Two patients (13.3%) were moderately ill, six (40.0%) were seriously ill and seven (46.7%) patients were critically ill.	All patients received TCZ. Dosing was not standardised and TCZ was administered with or without methylprednisolone at various doses.	There were 3 deaths (3 of 7 critically ill patients), 2 disease aggravations and 10 patients who were clinically stabilized. CRP decreased significantly from baseline 126.9mg/L (range 10.7 - 257.9 mg/L) ($p < 0.01$) IL-6 baseline values ranged between 16.4 pg/mL and 627.1 pg/mL (2 to nearly 90 times higher than normal). Serum IL-6 was reported to increase after the first dose of TCZ (10 patients) and persistently decreased in 1 patient when administered with methylprednisolone. Four critically ill patients, where therapy failed, demonstrated a persistent and dramatic increase in IL-6 levels.

Published, peer reviewed Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H[10] Effective Treatment of Severe COVID-19 Patients with Tocilizumab http://www.chinaxiv.org/abs/202003.00026	Retrospective case series Period: Feb 5 to Feb 14, 2020	Setting: China, Anhui Province Patients: 21 severe and critical COVID-19 patients. A severe case was defined if any of the following conditions was met: (1) respiratory rate ≥ 30 breaths/min; (2) SpO2 ≤ 93% while breathing room air; (3) PaO2/FiO2 ≤ 300 mmHg. A critical case was diagnosed if any of the following circumstances: (1) respiratory failure requiring mechanical ventilation; (2) shock; (3) combined with other organ failure, requiring ICU admission. Average age was 56.8 ± 16.5 years (range from 25 to 88 years). 18 patients were male (85.7%), three were female (14.3%). 17 patients (81.0%) were assessed as severe and 4 (19.0%) as critical. Eighteen patients (85.7%) received tocilizumab once, and 3 patients (14.3%) had a repeat within 12 hours due to fever.	TCZ administered as a single 400 mg dose. Other treatment included lopinavir, methylprednisolone, other symptom relievers and oxygen therapy.	The study focused on changes in body temperature, respiratory function, and CT findings before and after treatment with tocilizumab. Temperature returned to normal in all 21 patients on Day 1 after tocilizumab dose. Fifteen of the 20 patients (75.0%) had lowered their oxygen intake and one patient did not require further oxygen therapy. CT scans manifested that the lung lesion opacity absorbed in 19 patients (90.5%). The percentage of lymphocytes in peripheral blood, which decreased in 85.0% patients (17/20) before treatment (mean, 15.52 ± 8.89%), returned to normal in 52.6% patients (10/19) on the fifth day after treatment. Abnormally elevated C-reactive protein decreased significantly in 84.2% patients (16/19). The average time to discharge was 13.5 days after treatment for 19 patients. The remaining 2 patients were recovering well. No obvious adverse reactions were observed.

Appendix 1: Search strategy

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)