CADTH COVID-19 PANDEMIC

COVID-19 CADTH TECHNOLOGY REVIEW

Tocilizumab for the Treatment and Prevention of COVID-19: A Review of Clinical Effectiveness

This report was published on August 25, 2020.

To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly

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Abbreviations

COVID-19	coronavirus disease-2019
ICU	intensive care unit
SARS-CoV-2	acute respiratory syndrome coronavirus 2
Std	standard
TCZ	tocilizumab

Context and Policy Issues

Coronavirus disease -19 (COVID-19), caused by the novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in China in 2019, and then it spread world-wide resulting in a pandemic.[1-4] The clinical manifestation of COVID-19 infection is heterogeneous, ranging from no symptoms to severe pneumonia with respiratory failure that may require invasive mechanical ventilation and may lead to death.[2] Although COVID-19 appears to mainly target the pulmonary system, it may also affect other organs such as the kidney, gastrointestinal tract and the nervous system.[1] It is a highly contagious disease and there is an urgent need to find an appropriate treatment to combat the disease.[2] Different treatment options such as corticosteroids, hydroxychloroquine, lopinavir, ritonavir, remdesivir and tocilizumab are being investigated. Laboratory results of patients with severe COVID-19 infection showed an increase in pro-inflammatory cytokines, among which interlukin-6 (IL-6) played a major role.[5] Hence, it was thought that blocking the IL-6 pathway may reduce the inflammatory response to COVID-19.[5]

Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody that is an antagonist to the IL-6 receptor. It was reported that TCZ is used for severe rheumatoid arthritis and life-threatening cytochrome release syndrome.[2,3] TCZ may be a potential treatment option for COVID-19 infection.

The purpose of this report is to review the evidence on the clinical effectiveness of TCZ for the treatment and prevention of COVID-19 disease.

Research Question

What is the clinical effectiveness of tocilizumab for the treatment and prevention of coronavirus disease (COVID-19)?

Key Findings

One systematic review and five non-randomized, retrospective cohort studies were identified, that reported on treatment effects with tocilizumab (TCZ) in patients with COVID-19.

Findings were inconsistent with respect to mortality, survival, intensive care unit admissions, need for invasive mechanical ventilation, and duration of hospital stay, for tocilizumab (TCZ) compared with no TCZ. No statistically significant between group difference was found with respect to the proportion of patients discharged or for clinical

improvement with TCZ compared with no TCZ. Findings were inconsistent with respect to occurrence of adverse events or serious adverse events for TCZ compared with no TCZ. Findings need to be interpreted with caution, considering the limitations (such as evidence base of limited quality and quantity, inconsistencies in the findings, and lack of long-term data).

Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were tocilizumab and COVID-19. No search filters were applied to limit retrieval by study type. The search was also limited to English language documents published between January 1, 2019 and July 23, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Individuals with confirmed or suspected COVID-19 or those at risk of infection
Intervention	Tocilizumab (used as a treatment or as a prophylactic; alone or in combination with other therapies)
Comparator	No treatment; placebo; standard care; other active treatments (e.g., remdesivir)
Outcomes	Clinical effectiveness (e.g., mortality, length of hospital stay, severity of clinical symptoms, viral load, safety [e.g., rate of adverse events])
Study Designs	Health technology assessment, systematic review, randomized controlled trial, and non-randomized studies

COVID-19 = coronavirus disease 2019.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2019. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Publications that were preliminary reports, not peer-reviewed were excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[6] for systematic reviews, and the Downs and Black checklist[7] for non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 572 citations were identified in the literature search. Following screening of titles and abstracts, 543 citations were excluded and 29 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 29 potentially relevant articles, 23 publications were excluded for various reasons, and six publications met the inclusion criteria and were included in this report. These comprised one systematic review,[8] and five non-randomized studies.[3,9-12] Appendix 1 presents the PRISMA[13] flowchart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

One systematic review,[8] and five non-randomized studies[3,9-12] were selected. The primary studies included in the selected systematic review are listed in Appendix 5. The characteristics of the included publications are summarized below. Additional details are provided in Appendix 2, Table 2 (systematic review) and Table 3 (primary studies).

Study Design

In the included systematic review,[8] two databases were searched; search dates were not reported. It had a broad objective and assessed various treatment modalities for COVID-19 and only studies on TCZ which were relevant for this current report are described here. It included six relevant non-randomized studies comprising two prospective studies and four retrospective studies, published in 2020.

The five included non-randomized studies[3,9-12] were retrospective cohort studies.

Country of Origin

The included systematic review,[8] was published in 2020 from USA.

The five included non-randomized studies[3,9-12] were published in 2020 from Italy,[3,9,12] France,[10] and USA.[11]

Patient Population

The systematic review,[8] involved patients with COVID-19 infection. The number of patients in the relevant included studies ranged between 42 to 1229; patient characteristics were not presented.

The five non-randomized studies[3,9-12] included in this report involved hospitalized, adult patients with severe COVID-19 related symptoms, and the total number of patients in the individual studies ranged between 46 and 544. The median patient age varied between 59 years and 67 years in three studies[3,9,12] and the mean age was 60 years and 73 years in two studies.[10,11] The proportion of females varied between 14% and 34% in four studies,[3,9,11,12] and was not reported in one study.[10] In all the studies, the patients had other comorbidities (these included one or more conditions such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, cardiovascular disease, and malignancies).

Interventions and Comparators

The systematic review,[8] compared TCZ with control treatment. Details of control treatment were presented for two studies (hydroxychloroquine, azithromycin, heparin deep vein thrombosis prophylaxis in one study and hydroxychloroquine and lopinavir/ritonavir for another study); and not for the remaining four studies.

In the five included primary studies,[3,9-12] TCZ plus standard treatment (TCZ + Std) was compared with standard treatment (Std). Standard treatment comprised various combinations of drugs such as hydroxychloroquine, azithromycin, corticosteroids, anticoagulants, lopinavir, ritonavir, and remdesivir.

Outcomes

Outcomes reported included mortality,[3,9-12] survival,[8] intensive care unit (ICU) admission,[8,10] need for mechanical ventilation,[3,9,10] hospital stay,[10-12] discharge,[9,10] clinical improvement (i.e. proportion of patients discharged, or decrease in requirement for supplemental oxygen, invasive mechanical ventilation, or extra-corporeal membrane oxygen),[9] adverse events,[3,8,9,11,12] and serious adverse events.[3,9,12]

Follow-up time was not reported in the systematic review.[8] In the five primary studies, the mean follow-up time ranged between nine days and 55 days in four studies,[3,9,10,12] and follow-up time was not reported in the fifth study.[11]

Summary of Critical Appraisal

An overview of the critical appraisal of the included publications is summarized below. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 4 (systematic review) and Table 5 (primary studies).

In the included systematic review,[8] the objective was stated, two databases were searched, selection of studies was described, a list of included studies were provided, and the authors mentioned that there were no conflicts of interest. This systematic review had several limitations: a list of excluded studies was not presented, it was unclear if article selection, data extraction or quality assessment were done in duplicate, details of the study characteristics were lacking, and publication bias does not appear to have been conducted, hence the potential for missing studies and error in data extraction cannot be ruled out. Of note, this systematic review had a broad objective to assess treatment options for COVID-19 infection, and of the 26 studies selected, six studies were relevant for this report. These six studies were non-randomized studies with the majority being retrospective studies, which have inherent limitations. As patient characteristics were not reported, it was unclear if there were differences in patient characteristics in the studies included in the systematic review hence the potential of findings being impacted due to differences in patient characteristics cannot be ruled out.

In the five included primary studies[3,9-12] the objective, and the inclusion and exclusion criteria were stated; the patient characteristics, interventions, and outcomes were described; and the study authors mentioned that there were no conflicts of interest. All these studies were non-randomized, retrospective studies. Sample size calculation does not appear to have been conducted, hence it is unclear if the studies had the appropriate sample size to detect a difference between groups.

As the relevant studies (those included in the systematic review[8] or the included primary studies[3,9-12]) were non-randomized, there is potential of confounding due to unmeasured parameters which could impact findings. The studies were not blinded hence potential for performance bias and detection bias with respect to subjective outcomes such as clinical changes cannot be ruled out. The majority of the primary studies included in this report were retrospective studies, hence there is potential for all relevant data not being recorded. There were differences in patient characteristics (such as Charleston comorbidity index, vital signs, or presenting symptoms in the two groups (TCZ group and comparator group) in two studies[10,11] which could impact findings; no adjustments appear to have been made to minimize the impact on findings. In two studies[9,12] the patient characteristics reported were not statistically significantly different between the two groups; however, it is unknown if there were any differences in unmeasured parameters which could impact findings. In one study[3] the patient characteristics reported were not matched in the two groups but adjustments were made to minimize the impact of the reported characteristics on findings; however, differences in unmeasured parameters which may not have been considered in the adjustment, could still impact findings.

Summary of Findings

The main findings are summarized below. Details of the study findings and authors' conclusions are presented in Appendix 4, Table 6 (systematic review) and Table 7 (primary studies).

Clinical Effectiveness of Tocilizumab (TCZ)

One systematic review,[8] and five non-randomized, retrospective studies[3,9-12] reported on treatment effects with TCZ in patients with COVID-19 infection. All five non-randomized studies[3,9-12] reported on hospitalized adult patients; the systematic review[8] did not specify the patient population.

Survival or Mortality

The systematic review,[8] showed inconsistent survival results; with three non-randomized studies reporting increased survival with TCZ compared with control, and three non-randomized studies reporting no difference in survival between the two groups (results were described narratively, no numerical data were reported). Follow-up times were not reported.

The five non-randomized studies[3,9-12] showed inconsistent results with respect to mortality with TCZ + Std compared with Std alone; mortality was lower in the TCZ + Std group and the between group difference was statistically significant ($P < 0.05$) in two studies[3,12] and there was no statistically significant difference between treatment groups ($P > 0.05$) in three studies.[9-11]

Intensive Care Unit (ICU) admission

The systematic review,[8] reported that for TCZ compared to control, there was no statistically significant between group difference with respect to ICU admission (based on one non-randomized study).

One non-randomized study[10] reported that the proportion of patients admitted to the ICU was statistically significantly ($P < 0.05$) lower with TCZ + Std compared with Std alone.

Need for Invasive Mechanical Ventilation

The need for invasive mechanical ventilation in the TCZ + Std group compared to the Std group was numerically lower in one study[9] (statistical significance of the difference was not reported); statistically significantly ($P < 0.05$) lower in the second study,[10] and in the third study[3] the between group difference was not statistically significant ($P > 0.05$)

Clinical Improvement

One study[9] reported that the between group difference in clinical improvement (i.e. proportion of patients discharged, or decrease in requirement for supplemental oxygen, invasive mechanical ventilation, or extra-corporeal membrane oxygen) with TCZ + Std compared to STD alone was not statistically significant.

Hospital Stay or Discharge

Duration of hospital stay was reported in three studies,[10-12] and results were inconsistent. In two studies[10,11] the between group difference in hospital stay was not statistically significant ($P > 0.05$) for TCZ + Std compared with Std alone. In the third study[12] the duration of hospital stay was statistically significantly ($P < 0.05$) longer with TCZ + Std compared with Std alone.

The proportion of patients discharged from hospital was reported in two studies;[9,10] both studies showed that the between group difference in the proportion of patients discharged was not statistically significant ($P > 0.05$) in the TCZ + Std group compared with Std group.

Adverse Events

Adverse events were reported in one systematic review,[8] and four non-randomized studies.[3,9,11,12] The systematic review,[8] indicated that the included studies did not report any associated side effects with TCZ compared with standard therapy (the authors did not clearly specify if all or some of the included studies reported this outcome). Of the four non-randomized studies,[3,9,11,12] one study[9] comparing TCZ + Std with Std found that the between group difference was not statistically significant with respect to bacteremia and pulmonary thrombosis, and there was statistically significantly ($P < 0.05$) more transitory neutropenia with TCZ. The second study[3] found new infections were statistically significantly ($P < 0.05$) more with TCZ + Std compared with Std. The third study[11] found that bacteremia was statistically significantly ($P < 0.05$) more with TCZ + Std compared with Std, and for fungemia the between group difference was not statistically significant. The fourth study[12] reported occurrence of infections but did not clearly indicated in which group of patients.

Serious adverse events were reported in three non-randomized studies;[3,9,12] comparing TCZ + Std to Std; results were inconsistent and statistical significance of the between group difference was not reported.

Limitations

The evidence base is of limited quality. Most of the studies were non-randomized retrospective studies which have inherent limitations. There may be differences between patients who receive TCZ and those who do not, which could affect their outcomes. Though in some studies, the reported characteristics did not appear to be different between the groups, there may be confounding due to unmeasured parameters as the studies were non-randomized studies. In the studies, TCZ plus standard treatment was compared with

standard treatment alone; standard treatment comprised several drugs. It was unclear if there was variability in the drugs and dosages used for standard treatments for individual patients in the study, hence the impact on findings, if any, was unclear.

Not all outcomes were reported in all the studies. No long-term studies were identified hence the long-term effects of treatment with TCZ for patients with COVID-19 is unknown. No studies specifically comparing TCZ with another active drug (i.e., both intervention and comparator drugs on a background of standard therapy) were identified. No studies regarding TCZ for the prevention of COVID-19 were identified.

None of the studies were conducted in Canada, hence generalizability of the findings to the Canadian setting is unclear. However, the studies were conducted in developed countries, so the impact of the settings on generalizability to the Canadian context may not be very great.

Conclusions and Implications for Decision or Policy Making

One systematic review,[8] and five nonrandomized, retrospective cohort studies[3,9-12] reported on treatment effects with TCZ compared with no TCZ, in patients with COVID-19 infection. All five non-randomized studies[3,9-12] reported on hospitalized adult patients; the systematic review[8] did not specify the patient population. Not all publications reported all outcomes. Mortality or survival was reported in all six included publications,[3,8-12] ICU admission was reported in two publications,[9,10] need for mechanical ventilation was reported in three publications,[3,9,10] duration of hospital stay was reported in three publications,[10-12] proportions of patients discharged were reported in two publications,[9,10] clinical improvement in one publication,[9] adverse events were reported in five publications,[3,8,9,11,12] and serious adverse events were reported in two publications.[3,9] Findings were inconsistent with respect to mortality, survival, ICU admissions, need for invasive mechanical ventilation, and duration of hospital stay, for TCZ compared with no TCZ. No statistically significant between group difference was found with respect to the proportion of patients discharged or for clinical improvement with TCZ compared with no TCZ. Findings were inconsistent with respect to occurrence of adverse events or serious adverse events for TCZ compared with no TCZ.

Findings need to be interpreted with caution, considering the limitations (such as evidence base of limited quality and limited quantity, inconsistencies in the findings, and lack of long-term data). Many of the authors of the studies included in this report concluded that randomized controlled trials would be needed to confirm their findings.

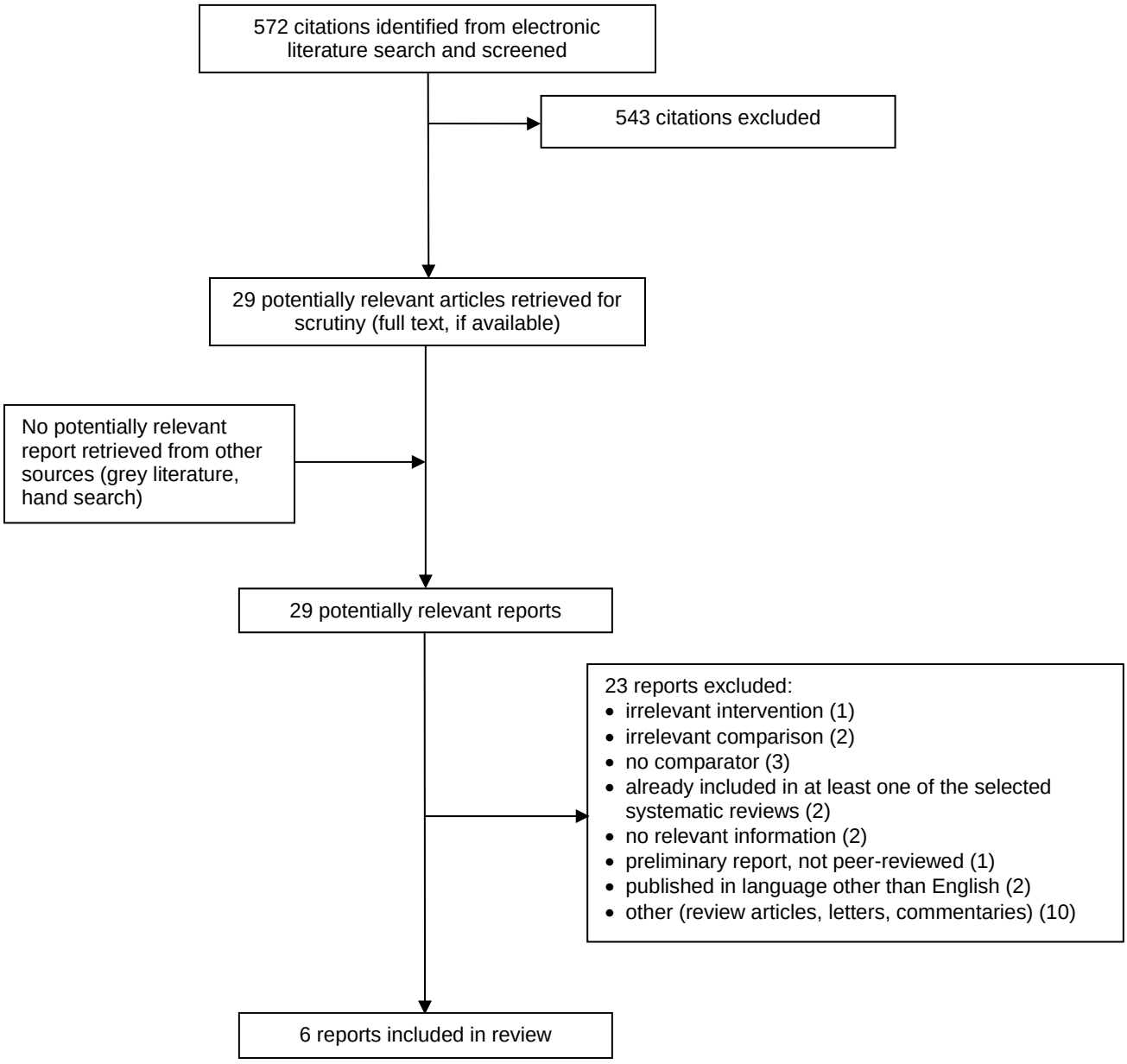
One phase III randomized controlled trial (COVACTA) on treatment with TCZ in hospitalized patients with severe COVID-19 associated pneumonia, recently reported in a press release that there was no statistically significant difference in clinical status (primary outcome) between TCZ compared with placebo (both groups received standard of care as well).[14] In addition, it was reported that there were no statistically significant between group differences in mortality (up to four weeks), or ventilator free days. Also, at four weeks, the rates of infections were 38.3% and 40.6% in the TCZ and placebo groups respectively; and the rates of serious adverse events were 21.0% and 25.9% in the TCZ and placebo groups, respectively. The results of this trial have not been published at the time this report was written and are not included in this report.

Future research with well-designed prospective studies and randomized controlled trials with long-term follow-up, are needed to evaluate the role of TCZ in the treatment of patients with COVID-19 infection. Also, assessing the effectiveness of TCZ in different subgroups (such as different age groups, patients with and without underlying comorbidities, various ethnicities) may be useful in identifying patients who are likely to benefit from the treatment. A CADTH report[15] on ongoing COVID-19 trials investigating various drugs, listed a number of ongoing trials on TCZ in adult patients. These are all randomized controlled trials comparing TCZ with placebo or an active drug (siltuximab, anakinra, deferoxamine, or methylprednisolone). The majority of the trials are on hospitalized adult patients with severe COVID-19 infection; one trial included patients with moderate COVID-19 infection as well. One randomized controlled trial involving patients with moderate COVID-19 infection has been planned but patients have not been recruited yet. These trials may provide more insights into the treatment effects of TCZ.

References

1. Athari SZ, Mohajeri D, Nourazar MA, Doustar Y. Updates on coronavirus (COVID-19) and kidney. *J Nephropathol.* 2020;9(4).
2. Alzghari SK, Acuna VS. Supportive Treatment with Tocilizumab for COVID-19: A Systematic Review. *J Clin Virol.* 2020;127:104380.
3. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol.* 2020.
4. Capra R, De Rossi N, Mattioli F, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *Eur J Intern Med.* 2020;76:31-35.
5. Colaneri M, Bogliolo L, Valsecchi P, et al. Tocilizumab for Treatment of Severe COVID-19 Patients: Preliminary Results from SMAtteo COvid19 REgistry (SMACORE). *Microorganisms.* 2020;8(5).
6. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.
7. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384.
8. Siordia JA, Yoshino K, Ulhaque A, Kumar S, Bernaba M, Bergin E. Systematic and Statistical Review of Coronavirus Disease 19 Treatment Trials. *SN Compr Clin Med.* 2020.
9. Campochiaro C, Della-Torre E, Cavalli G, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med.* 2020;76:43-49.
10. Klopfenstein T, Zayet S, Lohse A, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. *Med Mal Infect.* 2020.
11. Rojas-Marte GR, Khalid M, Mukhtar O, et al. Outcomes in Patients with Severe COVID-19 Disease Treated with Tocilizumab - A Case- Controlled Study. *QJM.* 2020.
12. Rossotti R, Travi G, Ughi N, et al. Safety and Efficacy of Anti-Il6-Receptor Tocilizumab Use in Severe and Critical Patients Affected by Coronavirus Disease 2019: A Comparative Analysis. *J Infect.* 2020;08:08.
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
14. F. Hoffmann-La Roche Ltd. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. 2020; https://www.roche.com/investors/updates/inv-update-2020-07-29.htm. Accessed 2020 Aug 21.
15. Ongoing Trials of Drugs in the Prevention and treatment of COVID-19. *(CADTH health technology review)*. Ottawa (ON): CADTH; 2020 Aug: https://cadth.ca/sites/default/files/covid-19/hc0006-005-ddt-table-drugs.pdf. Accessed 2020 Aug 20.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Siordi,[8] 2020, USA. Funding: There was no mention of funding; the authors declared that there were no conflicts of interest	Systematic review Two databases (PubMed, and Google Scholar) were searched. Search date not presented. It included 26 studies, of which 6 non-randomized studies were relevant to this report (2 prospective and 4 retrospective). Inclusion criteria: Studies with a control (placebo, standard therapy, or another medication). Exclusion criteria: Studies without a control, or in vitro or animal studies. Aim: To assess the evidence regarding treatments for COVID-19.	Patients with COVID-19 infection N (range): 42 to 1229 Age: NR % Female: NR Comorbidities: NR	TCZ vs Control Control: For 1 study: hydroxychloroquine, azithromycin, heparin DVT prophylaxis. For another study: hydroxychloroquine and lopinavir/ritonavir For the remaining 4 studies: NR Doses: NR	Survival, ICU admission. Side effects Follow-up: NR

DVT = deep vein thrombosis; ICU = intensive care unit; NR = not reported; TCZ = tocilizumab.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Campochiaro,[9] 2020, Italy	Retrospective cohort study Setting: San Raffaele Hospital in Milan, Italy Exclusion criteria: Patients with bacterial infection, history of diverticular disease, neutropenia, ALT & AST levels exceeding 5 times the upper limit of the normal range, and concomitant use of other immunosuppressive	Patients hospitalized for COVID-19. All patients needed NIV and/or high-flow supplemental oxygen at baseline. N = 65 (32 in TCZ[a], 33 in Std) Age (years) (median [IQR]): 64 (53 to 75) in TCZ, 60 (55 to 75.5) in Std; P = 0.52 % Female: 9% in TCZ, 18% in Std; P = 0.47	(TCZ+ Std) versus Std. TCZ (dose 400 mg) was administrated intravenously. In case of respiratory worsening (defined as need to start NIV or to start mechanical ventilation) a second dose of TCZ (400 mg) was given after 24 hours. Std comprised hydroxychloroquine 400 mg daily,	Mortality, discharge from hospital, need for invasive mechanical ventilation, clinical improvement. Adverse events, serious adverse events. Follow-up: 28 days

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	biologic drugs or corticosteroids were excluded. Aim: To assess the safety and efficacy of TCZ in severe COVID-19 patients	PaO_2/FiO_2 ratio (median [IQR]): 107 (82 to 181) in TCZ, 124 (91 to 172) in Std; P = 0.40 Comorbidities: 62% in TCZ, 61% in Std. (Comorbidities included one or more of the following: smoking, CKD, arterial hypertension, COPD, cancer, T2DM, CAD; P = NS for each of the comorbid conditions) Duration of symptoms (days) (median [IQR]): 11 (8 to 14) in TCZ, 9 (8 to 10) in Std; P =0.14	lopinavir/ritonavir 400/100 mg twice daily, ceftriaxone 2 g for 6 days, azithromycin 500 mg daily until a urine test for L. pneumophila was negative, anti-coagulation prophylaxis with enoxaparin 4000 UI subcutaneously once daily.	
Guaraldi,[3] 2020, Italy Funding: None. Also, the authors reported that there were no conflicts of interest	Retrospective cohort study Setting: Tertiary care centers in Bologna and Reggio Emilia in Italy. Exclusion criteria for the use of TCZ: coexistent infection; a PaO_2/FiO_2 ratio greater than 300 mm Hg; chronic or current glucocorticoid use; history of severe allergic reactions to monoclonal antibodies; neutrophils less than 500 per mcL or platelets less than 50 × 10^9; active diverticulitis, inflammatory bowel disease, or another symptomatic GI tract condition that might predispose patients to bowel perforation; severe impairment in haematological, renal, or liver function	Adult patients with severe COVID-19 pneumonia. N = 544 (179 in TCZ[a], 365 in Std Age (years) (median [IQR]): 64 (54 to 72) in TCZ, 69 (57 to78) in Std; P = 0.006 % Female: 29% in TCZ, 36%, in Std; P = 0.088 PaO_2/FiO_2 ratio (mm Hg) (median [IQR]): 169 (106 to 246) in TCZ, 277 (191 to 345) in Std; P = < 0.0001 SOFA score (median [IQR]): 3 (2 to 4) in TCZ, 2 (0 to 3) in Std; P = 0.0004 Duration of symptoms (median [IQR]): 12 (6 to 17) in TCZ, 8 (4 to 14) in Std; P = 0.0017	(TCZ +Std) vs Std TCZ was given intravenously or subcutaneously TCZ (intravenous): 8mg/kg body weight (up to a maximum of 800mg) was given twice at a12h interval. TCZ (subcutaneous): 324 mg in total. Std: supplemental oxygen, hydroxychloroquine, azithromycin, lopinavir-ritonavir (or darunavir-cobicistat), and low molecular weight heparin	Mortality, need for invasive mechanical ventilation. Adverse events, serious adverse events Follow-up (days) (median [IQR]): 12 (6 to 17) for TCZ, 8 (4 to 14) for Std

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	Aim: To assess the role of TCZ in the treatment for patients with severe COVID-19 pneumonia			
Klopfenstein,[10] 2020, France. Funding: Not reported. The authors declared that there were no conflicts of interest.	Retrospective cohort[b] study. Setting: Nord Franche-Comté Hospital, France Exclusion criteria: Patients with moderate disease, hospitalized less than 48 hours or did not receive standard treatment were excluded Aim: To assess treatment with and without TCZ	Hospitalized adult patients with severe COVID-19 infection. N = 46 (20 in TCZ[a], 25 in Std. Age (years) (mean [range]): 76.8 (52 to 93) in TCZ, 70.7 (33 to 96) in Std; P = 0.141. % Female: Not reported. Charleston comorbidity index (mean [range]):5.3 (I to 10) in TCZ, 3.4 (0 to 9) in Std; P = 0.014 Comorbidities (such as hypertension, cardiovascular disease, diabetes mellitus, COPD, immunosuppression, and malignancy) were not statistically significant between the two groups.	(TCZ +Std) vs Std TCZ: 1 or 2 doses Std: hydroxychloroquine or lopinavir-ritonavir therapy and antibiotics, and less commonly corticosteroids	Composite outcome (death and/or ICU admission), death, ICU admission, need for invasive mechanical ventilation, discharge, hospital stay. Follow-up: April 1 to April 24 (i.e. up to 24 days) for TCZ; and March 1 to April 24 (i.e. up to 55 days) for Std.
Rojas-Marte,[11] 2020, USA. Funding: Not reported. The authors declared that there were no conflicts of interest regarding publication of the article.	Retrospective cohort[b] study Setting: Maimonides Medical Center (a tertiary care teaching hospital in Brooklyn, USA Exclusion: Patients who died within 24 hours of admission, and those included in clinical trials with other biologic agents or convalescent plasma were excluded.	Hospitalized adult patients with severe to critical COVID-19 infection. N = 193 (96 in TCZ[a], 97 in C) Age (years) (mean ± SD): 58.8 ± 13.6 in TCZ, 62.0 ± 14. % Female: 23% in TCZ, 35% in C. Comorbidities (such as hypertension,	TCZ versus C (no TCZ) TCZ: 1 dose administered. Both groups received other medications such as hydroxychloroquine, azithromycin, corticosteroids, dose anti-coagulation, remdesivir, and antibiotics for suspected bacterial infection)	Mortality, and hospital stay. Adverse events. Follow-up: not reported. Patients received TCZ between 8 March and 25 April.

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	Aim: To assess outcomes in patients with COVID-19, who had received TCZ under compassionate use.	diabetes, stroke, atrial fibrillation, heart failure, asthma, COPD) were not statistically significant between the two groups.	Doses not presented.	
Rossotti,[12] 2020, Italy. Funding: The authors reported that no specific funding support was planned for this study. The authors reported that there were no conflicts of interest.	Retrospective cohort[c] study Setting: Single center, at a hospital in the Lombardi region, Italy. Exclusion criteria: ALT > 5 x ULN; neutrophil cell count < 500 cell/mmc; platelet count < 50,000 cell/mmc; presence of an active bacterial infection or a complicated intestinal diverticulitis (including perforated diverticulitis); a positive pregnancy test; a positive HBsAg status; any concomitant disease not defined as "under control". (Abbreviations: ULN, mmc, were not explained by the authors) Aim: To assess the efficacy and safety of TCZ for treating severe or critical COVID-19 patients.	Hospitalized adult patients with severe to critical COVID-19 infection. N = 222 (74 in TCZ[a], 148 in Std) Age (years) (median [IQR]): 59 (51 to 71) in TCZ 59 (52 to 70) in Std; P = 0.865. % Female: 17.6% in TCZ, 18.9% in Std; P = 0.807. Charlson comorbidity index (median [IQR]): 2 (1 to 3) in TCZ, 2 (1 to 4); P = 0.631. Time duration between symptom onset and hospitalization (days) (median [IQR]): 7 (5 to 10) in TCZ, 6 (4 to 8) in Std	(TCZ +Std) vs Std TCZ dose was 8 mg/kg infused over 60 minutes (maximum dose of 800 mg). In case of fever persistence a second dose was given after 12 hours. Std: hydrochloroquine plus lopinavir/ritonavir or remdesivir according to regional recommendation, drug availability, and remdesivir compassionate use program.	Mortality, hospital stay. Adverse events and serious adverse events. Follow-up: up to 50 days (from graph). Patients received TCZ between 13 March and 3 April.

ALT = alanine aminotransferase; AST – aspartate aminotransferase; C = control; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; FiO2 = fractional inspired oxygen; GI = gastrointestinal; ICU = intensive care unit; IQR = interquartile range; mcl = microliter; NS = not significant; PaO2 = arterial oxygen partial pressure; SD = standard deviation; SOFA = Subsequent Organ Failure Assessment; Std = standard treatment; TCZ = tocilizumab; T2DM = type-2 diabetes mellitus; TCZ = tocilizumab.

[a] The intervention group TCZ indicates treatment with TCZ + Std.

[b] The authors indicated the study as a case-control study but it appears to be a cohort study.

[c] The authors did not specify study type but it appears to be a cohort study.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Review Using AMSTAR 2[6]

Strengths	Limitations
Siordi,[8] 2020, USA	
• The objective was clearly stated • Two databases (PubMed and Google Scholar) were searched. Search dates were not presented • Study selection was described, and a flow chart was presented • A list of included studies was provided • Characteristics of the included studies were briefly presented • It was reported that the authors had no conflicts of interest	• A list of excluded studies was not provided • Unclear if article selection was done in duplicate • Unclear if data extraction was done in duplicate • Unclear if quality assessment of the included studies was conducted • Details regarding study characteristics were lacking. • Publication bias does not appear to have been assessed

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2.

Table 5: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[7]

Strengths	Limitations
Campochiaro, [9] 2020, Italy	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • P values were mostly reported • The authors reported that there were no conflicts of interest	• The study was not a randomized controlled trial; it was a retrospective study; however, there were no statistically significant differences in patient characteristics (with respect to age, proportion of females, and proportion with comorbidities) between the different groups. • There was no blinding hence potential for performance bias and detection bias cannot be ruled out • Sample size calculation does not appear to have been conducted; it is possible that the study may be underpowered to detect a difference between groups
Guaraldi,[3] 2020, Italy	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • P values were mostly reported • The authors reported that there were no conflicts of interest	• The study was not a randomized controlled trial; it was a retrospective study, there were statistically significant differences in patient characteristics between the two groups. Cox regression analyses were conducted, and adjusted hazard ratios were presented • There was no blinding hence potential for performance bias and detection bias cannot be ruled out • Sample size calculation does not appear to have been conducted; however, the sample size used was large (544 patients)
Klopfenstein, [10] 2020, France	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • P values were mostly reported • The authors reported that there were no conflicts of interest	• The study was not a randomized controlled trial; it was a retrospective study. There were no statistically significant differences between the two groups with respect to age and comorbidities; however, the patients in the TCZ + Std group had a higher Charlson comorbidity index than those in the Std group. No adjusted results were presented. • There was no blinding hence potential for performance bias and detection biases cannot be ruled out • Sample size calculation does not appear to have been conducted.
Rojas-Marte,[11] 2020, USA	
• The objective was clearly stated • The inclusion and exclusion criteria were stated	• The study was not a randomized controlled trial; it was a retrospective study, there were statistically significant differences in patient characteristics (with respect to baseline symptoms such as shortness of breath, and myalgia; and vital signs such as oxygen saturation and

Strengths	Limitations
• Patient characteristics, intervention and outcomes were described. • P values were mostly reported • The authors reported that there were no conflicts of interest	respiratory rate) between the two groups, being higher in the TCZ group than in the Std group. • There was no blinding hence potential for performance bias and detection bias cannot be ruled out. • Sample size calculation does not appear to have been conducted.
Rossotti,[12] 2020, Italy	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • P values were mostly reported • The authors reported that there were no conflicts of interest	• The study was not a randomized controlled trial; it was a retrospective study. The authors mentioned that the groups were matched; the method of matching was not described. There were no statistically significant differences between the two groups with respect to age, sex, Charlson comorbidity index, and time from symptom onset to hospitalization; however, as the study was not randomized the potential for differences in unmeasured parameters cannot be ruled out. • There was no blinding hence potential for performance bias and detection bias cannot be ruled out. • Sample size calculation does not appear to have been conducted.

Std = standard; TCZ = tocilizumab.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Review

Main study findings	Authors' conclusion
Siordi,[8] 2020, USA	
Findings are from 6 studies (2 prospective and 4 retrospective) involving patients with COVID-19 Three studies (1 prospective and 2 retrospective) reported increased survival with TCZ compared with control, whereas three studies (1 prospective and 2 retrospective) described no difference in survival between the two groups. One retrospective study showed that there was no between group difference with respect to ICU admission. Side effects: The studies did not report any associated side effects with TCZ compared with standard therapy (it was unclear if all or some of the studies reported this outcome)	"Current medications do not show significant effect on COVID-19 viral clearance rates. Tocilizumab showed mixed results regarding survival. (page 1 of 12)"[8]

TCZ = tocilizumab.

Table 7: Summary of Findings of Included Primary Clinical Studies

Campochiaro,[9] 2020, Italy

Findings from a retrospective study involving 65 hospitalized patients with COVID-19

Outcomes with TCZ + Std compared with Std alone

Outcome	Percentage of patients with outcome		P value
	TCZ + Std N = 32	Std N = 33	
Discharge from hospital	63	49	0.32
Clinical improvement	69	61	0.61
Need for NIV and/or high flow supplemental oxygen	9	3	NR
Need for invasive mechanical ventilation or ECMO	0	3	NR
Need for mechanical ventilation	13	6	0.43
Death	16	33	0.15

Adverse events with TCZ + Std compared with Std alone

Outcome	Proportion (%) of patients with outcome		P value
	TCZ+Std N = 32	Std N = 33	
Bacteremia	13	12	0.99
Pulmonary thrombosis	6	9	0.99
Transitory increase in AST or ALT	15	18	0.99
Transitory neutropenia	16	0	0.02
Serious adverse events	25	27	NR

One patient in each group developed pneumothorax. No infusion related adverse events were reported.

"In our study, we did not observe clear improvements in patients receiving tocilizumab compared to standard management. Infectious adverse events require careful monitoring to evaluate long-term risks. The results of ongoing randomized placebo-controlled trials are eagerly awaited to establish the role of IL-6 blockade in severe COVID-19 patients, and whether tocilizumab therapy might be safely and effectively used for treating COVID-19. (p. 47 to 48)" [9]

Main study findings	Authors' conclusion
Guaraldi,[3] 2020, Italy	
Findings from a retrospective study involving 544 hospitalized patients with severe COVID-19 pneumonia *Outcomes with TCZ + Std compared with Std alone* **Outcome** | **Proportion (%) of patients with outcome: TCZ+Std N = 179** | **Std N = 365** | **P value** Initiation of invasive mechanical ventilation | 18 | 16 | 0.41 Death | 7 | 20 | 0.0007 *Hazard ratio (HR) for the composite outcome (initiation of invasive mechanical ventilation or death)* for *TCZ + Std compared with Std as reference* Unadjusted HR (95% CI): 0.60 (0.43 to 0.84) Adjusted HR (95% CI): 0.61 (0.40 to 0.92) Using a Cox regression model. Adjustments made for age, sex, recruiting centre, duration of symptoms, and SOFA score. Unadjusted HR (95% CI): 0.54 (0.37 to 0.78) Adjusted HR (95% CI): 0.0.53 (0.31 to 0.89) Using a weighted Cox regression model. Adjustments made for age, sex, recruiting centre, duration of symptoms, SOFA score, use of steroids after baseline, and censoring using inverse probability weighting. *Hazard ratio (HR) for death (all-cause mortality)* for *TCZ + Std compared with Std as reference* Unadjusted HR (95% CI): 0.28 (0.15 to 0.50) Adjusted HR (95% CI): 0.38 (0.17 to 0.83) Using a Cox regression model. Adjustments made for age, sex, recruiting centre, duration of symptoms, and SOFA score. *Adverse events with TCZ + Std compared with Std alone* **Outcome** | **Number of patients (Proportion [%] of patients) with outcome: TCZ+Std N = 179** | **Std N = 365** | **P value** Overall new infections | 24 (13%) | 14 (4%) | <0.0001 Hepatitis B virus reactivation | 1 | 0 | NR Herpes simplex virus 1 reactivation | 4 | 0 | NR Serious adverse events (severe liver failure due to herpes simplex virus 1 reactivation) | <1% | NA | NR	"In conclusion, both intravenous and subcutaneous tocilizumab administration might be capable of reducing the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia. Although these results are encouraging, they should be confirmed in ongoing randomised studies. (p. 10)"[3]

Main study findings	Authors' conclusion

Klopfenstein,[10] 2020, France

Findings from a retrospective study involving 46 hospitalized adult patients with COVID-19 infection.

Outcomes with TCZ + Std compared with Std alone

Outcome	Proportion (%)[a] of patients with outcome		P value
	TCZ+Std N = 20	Std N = 25	
Death and/or ICU admission	25	72	0.002
Death	25	48	0.065
ICU admission	0	44	<0.001
Invasive mechanical ventilation	0	32	0.006
Discharge	55	44	0.463
Duration of hospitalization (days)	13 (4 to 32)	17 (5 to 41)	0.324
[a]Unless stated otherwise			

"Despite the small sample size and retrospective nature of the work, this result strongly suggests that TCZ may reduce the number of ICU admissions and/or mortality in patients with severe SARS-CoV-2 pneumonia. (p. 397)"[10]

Rojas-Marte,[11] 2020, USA

Findings from a retrospective study involving 193 hospitalized adult patients with severe to critical COVID-19 disease.

Outcomes with TCZ compared with control (no TCZ)

Outcome	Proportion (%)[a] of patients with outcome		P value
	TCZ N = 96	Control (no TCZ) N = 97	
Overall mortality	44.8	56.7	0.09
Mortality in non-intubated patients (excluding patients still in hospital)	6.1	26.5	0.024
Mortality in intubated patients (excluding patients still in hospital)	67.2	75	0.34
Hospital stay (excluding patients still in hospital) (days) (mean ± SD)	14.5 ± 8.8	16.5 ± 10.8	0.329
Bacteremia	12.5	23.7	0.04
Fungemia	4.2	3.1	0.72
[a]Unless stated otherwise			

"Our study showed a non-significant trend toward lower mortality in patients with severe to critical COVID-19 disease treated with tocilizumab. When intubated patients were excluded, those who received tocilizumab had a lower mortality. Randomized clinical trials are needed to confirm these and other findings and provide more information regarding dosing, short- and long-term adverse effects, and proper timing of administration. (p. 5)"[11]

Rossotti,[12] 2020, Italy.

Findings from a retrospective study involving 222 hospitalized, severe or critical, adult patients with COVID-19 infection.

Outcomes with TCZ + Std compared with Std alone (using Cox regression analysis)

Outcome	HR (95% CI)	P value
Mortality	0.499 (0.262 to 0.952)	0.035
Hospital stay	1.658 (1.088 to 2.524)	0.019

Adverse events

The authors reported that 24 (32.4%) patients experienced infectious complications (it was not specified in which patient group, but from the numbers reported it

"TCZ use resulted potentially effective on COVID-19 in terms of overall survival. Caution is warranted given the potential occurrence of adverse events. (p. 1)"[12]

Main study findings	Authors' conclusion
appears to be in the patients who were administered TCZ [n = 74]). There were 11 (14.9%) severe adverse events comprising 6 sepsis cases due to gram-negative bacteria, 2 sepsis cases due to gram-positive, 1 candidemia, 1 lung abscess, and 1epidural abscess, both needing surgical drainage.	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; ECMO = extracorporeal membrane oxygenation; HR = hazard ratio; ICU = intensive care unit; IL-6 = interleukin 6; NA = not applicable; NIV = non-invasive ventilation; NR = not reported; SD = standard deviation; SOFA = Subsequent Organ Failure Assessment; Std = standard treatment; TCZ = tocilizumab.

Appendix 5: Relevant Primary Studies Included in the Systematic Review[8]

Primary study citation
Capra et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020;76:31–5.
Colaneri et al. Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SMAtteo COvid19 Registry (SMACORE). Microorganisms. 2020;8:695.
Ip et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients – an observational study. MedRxiv. 2020.
Martinez-Sanz et al. Effects of tocilizumab on mortality in hospitalized patients with COVID-19: a multicenter cohort study. MedRxiv. 2020.
Rossi et al. Effect of tocilizumab in hospitalized patients with severe pneumonia COVID-19: a cohort study. MedRxiv. 2020.
Wadad et al. Improved survival outcome in SARs-CoV-2 (COVID-19) acute respiratory distress syndrome patients with tocilizumab administration. MedRxiv. 2020.

Appendix 6: Additional References of Potential Interest

Preliminary reports - Not Peer-Reviewed

Disclaimer from medRxiv: "Caution: Preprints are preliminary reports of work that have not been certified by peer review. They should not be relied on to guide clinical practice or health-related behavior and should not be reported in news media as established information."

Kaye AG, Siegel R. The Efficacy of IL-6 Inhibitor Tocilizumab in Reducing Severe COVID-19 Mortality: A Systematic Review **[non peer-reviewed preprint]**. *medRxiv*. 2020:2020.2007.2010.20150938.
https://www.medrxiv.org/content/10.1101/2020.07.10.20150938v1

Khan F, Fabbri L, Stewart I, Robinson K, Smyth AR, Jenkins G. A systematic review of Anakinra, Tocilizumab, Sarilumab and Siltuximab for coronavirus-related infections **[non peer-reviewed preprint]**. *medRxiv*. 2020:2020.2004.2023.20076612.
https://www.medrxiv.org/content/10.1101/2020.04.23.20076612v1

Kim MS, An MH, Kim WJ, Hwang T-H. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis of confounder-adjusted 20212 hospitalized patients **[non peer-reviewed preprint]**. *medRxiv*. 2020:2020.2006.2015.20132407.
https://www.medrxiv.org/content/10.1101/2020.06.15.20132407v1

Kimmig LM, Wu D, Gold M, et al. IL6 inhibition in critically ill COVID-19 patients is associated with increased secondary infections **[non peer-reviewed preprint]**. *medRxiv*. 2020:2020.2005.2015.20103531.
https://www.medrxiv.org/content/10.1101/2020.05.15.20103531v2

Moreno Garcia E, Rico Caballero V, Albiach L, et al. Tocilizumab is associated with reduction of the risk of ICU admission and mortality in patients with SARS-CoV-2 infection **[non peer-reviewed preprint]**. *medRxiv*. 2020:2020.2006.2005.20113738.
https://www.medrxiv.org/content/10.1101/2020.06.05.20113738v1

Narain S, Stefanov D, Chau AS, et al. Comparative Survival Analysis of Immunomodulatory Therapy for COVID-19 'Cytokine Storm': A Retrospective Observational Cohort Study **[non peer-reviewed preprint]**. *medRxiv*. 2020:2020.2006.2016.20126714.
https://www.medrxiv.org/content/10.1101/2020.06.16.20126714v1

Ramaswamy M, Mannam P, Comer R, Sinclair E, McQuaid DB, Schmidt ML. Off-Label Real World Experience Using Tocilizumab for Patients Hospitalized with COVID-19 Disease in a Regional Community Health System: A Case-Control Study **[non peer-reviewed preprint]**. *medRxiv*. 2020:2020.2005.2014.20099234.
https://www.medrxiv.org/content/10.1101/2020.05.14.20099234v1

Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19 **[non peer-reviewed preprint]**. *medRxiv.* 2020;03:03
https://www.medrxiv.org/content/10.1101/2020.05.29.20117358v1