EVIDENCE SUMMARY

Should Tocilizumab be used in the treatment of children with COVID-19 infection?

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Recommendation

We suggest the addition of tocilizumab to systemic steroids in patients with moderate to severe COVID-19 infection, particularly where there is evidence of systemic inflammation

Certainty of Evidence: Very Low
Strength of Recommendation: Weak

Consensus Issues
Although the evidence was based on 17 randomized controlled trials done in hospitalized adult patients with moderate to severe COVID-19, the panel voted for the use of tocilizumab as treatment for COVID-19 in children due to the significant benefit in all-cause mortality and need for mechanical ventilation.

Key Findings

There were no observational or randomized controlled trial (RCT) data on the effectiveness of tocilizumab for the treatment of acute COVID-19 infection in pediatric patients. Taking this into consideration, the review considered the effect of tocilizumab on adults with Covid-19 as indirect evidence for our chosen population basing it primarily on the recently updated Philippine Adult LCPG Phase II

Pooled results of 17 RCTs (n=9,649) which investigated the efficacy of tocilizumab among hospitalized adult patients with moderate to severe COVID-19 infection comparing to placebo and/or standard of care showed significant benefit in all-cause mortality and need for mechanical ventilation with no significant increase in the risk for adverse events and serious adverse events among those who received tociluzumab.. Adverse events reported were neutropenia, leukopenia, anxiety, arrhythmia, insomnia, stroke, constipation, pneumothorax, intracranial bleeding, and pulmonary embolism among others. In addition, co-administration with steroids demonstrated benefit with significant reduction in mortality.

Introduction

Some patients with COVID-19 develop a hyperinflammatory syndrome that is characterized by elevations in proinflammatory cytokines and multiorgan dysfunction also known as the immunopathology of SARS-CoV-2 infection. [2,3] Tocilizumab, a monoclonal anti-IL-6-receptor blocking antibody, has been proposed as a therapeutic agent to mitigate hyperinflammation associated with COVID-19. It has been utilized in children with cytokine release syndrome associated with CAR T-cell therapy including systemic and polyarticular juvenile idiopathic arthritis. [2,4]

FDA issued an emergency use authorization (EUA) for tocilizumab for the treatment of hospitalized adults and pediatric patients 2 years of age and older with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). [1,2] This review looks into the effectiveness of tocilizumab in the treatment of children with COVID-19 and MIS-C.

Review Methods

A systematic literature search was performed to identify relevant studies in PubMed, Cochrane Library, WHO trial Registry, ClinicalTrial.gov and Covid-19 NMA databases among others up to January 10, 2022. A preprint search was also done in medRxiv, chinaXiv and bioRxiv. The search strategy combined concepts related to tocilizumab, COVID-19, pediatrics, and children. MeSH and free text search were done using the following terms: Covid 19 (Coronavirus 19, SARS-Cov 2,); tocilizumab (Actemra, IL-6 receptor inhibitor, IL-6 receptor antagonist); Children (Pediatrics); Observational Studies, Meta-Analysis, and Randomized Clinical Trial. References listed in each identified study was manually searched for related articles to identify all eligible studies and minimize any potential publication bias. No language or journal type restriction was applied (Appendix 1). The inclusion criteria for this review were as follows:

Table 1. PICO criteria for tocilizumab and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Tocilizumab
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Mortality, need for ventilation or ICU stay, clinical improvement, adverse effects

Results

There were no observational or randomized controlled trial (RCT) retrieved on the effectiveness of tocilizumab for the treatment of acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C). In the absence of adequate data on children with acute COVID-19, outcome and safety data for adult patients were reviewed as indirect evidence. The Adult COVID-19 Living Clinical Practice Guidelines Phase II (Philippines) which was reviewed to be of good quality using AGREE II served as primary reference and was then supplemented with data from the Covid-19 NMA initiative (Appendix 3).

Two (2) new RCTS were added to the existing data from the Adult LCPG Phase II, both of which were evaluated to have low risk of bias using Cochrane ROB 2. Results were pooled and subgroup analyses on the effect of tocilizumab on mortality stratified according to oxygen requirement and co-administration of steroids were done.

Characteristics of Study Population, Interventions, and Comparators

Indirect evidence coming from 17 RCTs among adult patients were multicenter studies [5-21]. All of the trials reviewed were also included in the COVID-NMA Living Data [22]. Four (4) of the 17 trials were preprints [18-21]. Overall, a total of 9,649 patients were included in this meta-analysis, in which 5,319 and 4,330 patients were assigned to the tocilizumab and control groups, respectively. The population, drugs used, and methodology process were comparable in all included studies.

The study participants in all trials were 18 years old and above with clinically suspected or laboratory confirmed SARS-CoV-2 infection, with presence of pulmonary infiltrates, and with oxygen saturation of <94% on room air. Patients were excluded if the treating physician

determined that death was imminent and inevitable within 24 hours or if they had active tuberculosis or a bacterial, fungal, or viral infection other than SARS-CoV-2. Four (4) trials included elevated laboratory markers such as C-reactive protein (CRP), d-dimer and ferritin in their inclusion criteria [10-12,19]. Seven (7) trials excluded patients on mechanical ventilation at the start of the trial [7,9-11,16,18,19], while two (2) trials enrolled critical patients admitted in the intensive care unit who were receiving respiratory or cardiovascular organ support [9,18].

Patients allocated to the intervention group received tocilizumab as a single intravenous infusion over 60 minutes. The dose of tocilizumab was 8mg/kg/dose with a maximum dose of 800mg. A second dose could be given 12–24 hours later if, in the opinion of the attending clinician, the patient's condition had not improved or if fever persists after 24hours from the initial dose. The standard of care was used as comparator, and these were based on local practice and may or may not include the administration of low-dose glucocorticoids, anticoagulants, or anti-viral drugs (e.g., dexamethasone, aspirin, lopinavir/ritonavir, remdesivir, and hydroxychloroquine) on top of other supportive measures (Appendix 3).

Overall Quality of Evidence

The overall quality of evidence was rated very low. The population on all included studies are adults (>18 years old) and only serves as indirect evidence for our pediatric population. Other compounding reasons are the presence of serious risk of bias and imprecision. The included studies had serious risk of bias due to issues on performance bias, detection bias, and reporting bias. Blinding was only present in five out of the 17 included studies [7,11,17,19,21]. Moreover, there were noted differences in the administration of steroids, antivirals, and other supplementary medications used in the control group for some of the included studies (Appendix 2).

Efficacy Outcomes

Mortality Outcomes

Based on the pooled results of the 16 out of the 17 RCTs included, tocilizumab significantly reduced all-cause mortality at day 14 to day 90 follow-up compared to standard of care among adults (RR = 0.88, 95% CI 0.82-0.94; Low Certainty). Tocilizumab significantly reduced all-cause mortality at day 28 (RR 0.87, 95% CI 0.81-0.94; Low Certainty) but had no significant effect on mortality at day 90 (RR 0.89, 95% CI 0.76-1.02; Very Low Certainty). All results had low heterogeneity and low certainty of evidence except for 90-day mortality which has a very low certainty of evidence.

Subgroup analysis of mortality outcome according to oxygen requirement type did not show significant benefit across groups. These included those requiring oxygen supplementation (RR 0.88, 95% CI 0.75-1.04; Low Certainty); those requiring non-invasive ventilation (RR 0.89, 95% CI 0.79-1.00; Low Certainty); and those requiring invasive mechanical ventilation (RR 0.97, 95% CI 0.82-1.15; Very Low Certainty).

Subgroup analysis (n=6 studies) by co-administration of steroids demonstrated significant reduction in mortality (RR 0.80, 95% CI 0.66-0.97; Low Certainty). There was no observed benefit among patients who were not given steroids (RR 1.09, 95% CI 0.91-1.29).

Clinical Improvement

Pooled results (n=8 studies) showed no significant difference both in clinical improvement at day 28 (RR 1.06, 95% CI 0.99-1.12; Low Certainty) and in the time to clinical improvement (HR 1.11, 95% CI 0.99-1.25) among adult patients given tocilizumab compared to those who received standard of care. Clinical Improvement was evaluated by the patients' clinical, general, and

laboratory conditions and were determined by good consciousness, ameliorated dyspnea, stopped fever for 3 days, O2 saturation greater than 93%, normal range of urinary output, tolerated oral regimen (PO), blood pressure more than 10 millimeters of mercury (mmHg), respiratory rate and heart rate within normal limits and reduced CRP amount.

Need for Mechanical Ventilation

Pooled results of nine studies showed significant reduction in the need for mechanical ventilation among adult patients given Tocilizumab compared to standard of care (RR 0.78, 95% CI 0.68-0.89; Low Certainty).

Length of ICU Stay and Hospital Stay

There was no observed difference in the length of ICU stay (n=3) (MD -1.94 days, 95% CI -6.8 to 2.91; Very Low Certainty) and hospital stay (n=2) (MD -2.5 days, 95% CI -6.8 to 1.80; Very Low Certainty) in those given Tocilizumab compared to that of standard of care.

Time to Negative Conversion

Wang et.al presented data regarding time to negative conversion which showed no significant difference between those given Tocilizumab and those who only received standard of care with a median of 17days (IQR: 12-20 days) and 16 days (IQR:12-21.5 days) respectively [12]. This is similar with the results in the study done by Rosas 2021 (REMDACTA Trial) which showed an equivocal result [17].

Cure Rate

Cure followed the definition by the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (5th or updated version): (1) fever attenuated continuously for 7 days, (2) twice negative SARS-CoV-2 nucleic acid detections, (3) CT scan demonstrating chest effusion improved more than 50% when the patient is discharged from the hospital [12]. The study by Wang et.al. (2020) showed that the cure rate of the tocilizumab group tended to be higher than that of the control group (94.12% vs.87.10%), but the difference between the two groups was not statistically significant [RD 0.07 (95% CI 7.19% to –21.23%)] [12]. This is similar with the findings of Talaschian et.al [19].

Safety Outcomes

Adverse Events and Serious Adverse Events

Tocilizumab did not significantly increase the risk for adverse events (RR 1.03 95% CI 0.97-1.11; Very Low Certainty) and serious adverse events among adult patients (RR 0.92, 95% CI 0.77-1.08; Very Low Certainty). Common adverse events noted with tocilizumab were neutropenia, leukopenia, anxiety, arrhythmia, insomnia, stroke, and constipation. Serious adverse events observed were pneumothorax, intracranial bleeding, and pulmonary embolism among others.

Other Considerations (Evidence to Decision)

Tocilizumab, a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits the binding of IL-6 to both membrane and soluble IL-6 receptors, is being used as compassionate drug in the Philippines for various cancers and arthritis. Administration of this drug is through intravenous infusion for one dose with a maximum of two doses. The Presidential Executive Order 104 regulates the price of tocilizumab 200mg/10 ml, 10ml vial to P10,392.98 for wholesale price and P28,830.82 for retail price. Tocilizumab 400mg/20ml, 20ml vial is regulated at P20,581.45 for wholesale price and P28,830.84 for retail price. [23] Assuming the maximum dose of 800mg, the total drug regimen cost per patient per treatment course would be P57,661.68 (retail price) or a

little lower in price in children since the recommended dosage are as follows: <30kg: 12mg/kg/dose and for > or = 30kgs: 8mg/kg/dose.

There are currently no local feasibility studies for this drug and no studies assessing patients' values or acceptability of the drug

Recommendations from Other Groups

As of November 2021, US-NIH states that there are no pediatric data from placebo-controlled randomized clinical trials and limited data from observational studies to inform the development of pediatric-specific recommendations for the treatment of COVID-19 in children. Hence, there is insufficient evidence for the Panel to recommend either for or against the use of tocilizumab for hospitalized children with COVID-19 or MIS-C. If used, tocilizumab should be used in combination with dexamethasone. This is based on outcome and safety data for adult patients and the child's risk of disease progression [1].

The CPG Australian Guidelines for the Clinical Care of Patients with Covid-19 (2021) suggest to consider using tocilizumab for the treatment of COVID-19 in children and adolescents who require supplemental oxygen, particularly where there is evidence of systemic inflammation. (Conditional Recommendation) [24].

For local recommendation, the Philippine Infectious Disease Society of Pediatrics released a guide as of January 2022 wherein they suggest the use of Tocilizumab plus systemic steroids in patients showing rapid respiratory deterioration and/or requiring high doses of oxygen associated with elevated markers of inflammation [25].

Research Gaps

As of February 2, 2022, there is one ongoing trial specific on the effect of Tocilizumab on the pediatric population and is currently in the process of recruitment with an estimated completion date on January 2023.

The data specific for the use of Tocilizumab in children with Covid-19 are limited, derived mainly from clinical experiential accounts. A randomized clinical trial, if possible, is needed to further assess and evaluate optimal components of care in this particular patient population. Though their condition is similar to adult patients with Covid-19, the differences in other processes might affect the final outcome when studied strictly among the pediatric population.

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Appendix 1. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	("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 ("child" [MeSH Terms] OR "child" [All Fields] OR "children"[All Fields] OR "child s" [All Fields] OR "children s"[All Fields] OR "childrens" [All Fields] OR "childs"[All Fields])	01/02/22 10:03AM	19	15
CENTRAL	tocilizumab: "tocilizumab"[Supplementary Concept] OR "tocilizumab" [All Fields] covid 19: ("COVID-19" OR "COVID-19" [MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines" [MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing" [MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing" [MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT])) children: "child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child's"[All Fields] OR "children's"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]	01/02/22 2:13PM	24	12
COVID-NMA Initiative	Tocilizumab	01/02/22 6:30PM	17	17
Google Scholar	Tocilizumab AND COVID AND randomized trial AND Children	01/02/22 12:18PM	13	10

ClinicalTrials.gov	COVID-19, Investigational Trials, Tocilizumab With or without Children or Pediatrics *For ongoing studies	01/01/22 7:30PM	96	2
Chinese Clinical Trial Registry	COVID Tocilizumab	01/01/22 8:00AM	3	0
EU Clinical Trials Register	COVID Tocilizumab	01/01/22 10:32AM	6	4
Japan Primary Registries Network/ NIPH Clinical Trials Search	COVID Tocilizumab	01/01/22 2:30PM	0	0
chinaxiv.org	COVID Tocilizumab	01/01/22 9:45AM	1	0
Medrxiv.org	COVID Tocilizumab	01/01/22 11:50AM	5	5
Biorxiv.org	COVID Tocilizumab	01/01/22 12:42PM	0	0

Appendix 2. Characteristics of Included Studies

Title/Author	Study design	Country	Population	Intervention Group(s)	Control	Outcomes
Horby 2021 RECOVERY N=4116	Open label RCT	Multicenter; United Kingdom	Adult patients >18 years old with suspected or confirmed Covid.	Tocilizumab 8mg/kg	Standard of care	-All-cause mortality at day 28 -Time to discharge -Receipt of invasive mechanical ventilation -Use of non-invasive respiratory support -Time to successful cessation of invasive mechanical ventilation -Use of renal dialysis/hemofiltration -Major cardiac arrhythmia -Serious adverse events
Gordon 2020 REMAP-CAP N=755	Adaptive RCT	Multicenter; United Kingdom, France, the Netherlands, Australia	ICU admitted critical Covid-19 patients AND receiving respiratory or cardiovascular organ support	Group 1: Tocilizumab 8 mg/kg Group 2: Sarilumab	Standard of care	-Respiratory and cardiovascular organ support-free days -Survival -Time to ICU discharge -Time to hospital discharge -WHO scale at day 14 -Progression to invasive mechanical ventilation, ECMO or death -Serious adverse events
Hermine 2020 N= 131	Open label RCT	Multicenter; France	Moderate, severe or critical Covid-19 patients with O2 levels of 3 L/min or higher but without noninvasive ventilation (NIV) or mechanical ventilation (MV).	Tocilizumab 8 mg/kg	Standard of care	-Mortality on day 4 and day 14 -Mechanical ventilation on day 4 and day 14 -Clinical status (WHO CPS) at day 7 and day 14 -Overall survival -Time to discharge -Time to oxygen supply independency -C-reactive protein levels -Adverse events
Rosas 2020 COVACTA N=452	Double-blind, placebo controlled RCT	Canada, Denmark, France, Germany, Italy, Netherland,Spain, UK, USA	Severe Covid-19 patients	Tocilizumab 8mg/kg	Placebo	-Clinical status at day 28 -Mortality -Ventilator free days -Time to improvement -Time to hospital discharge -Adverse events

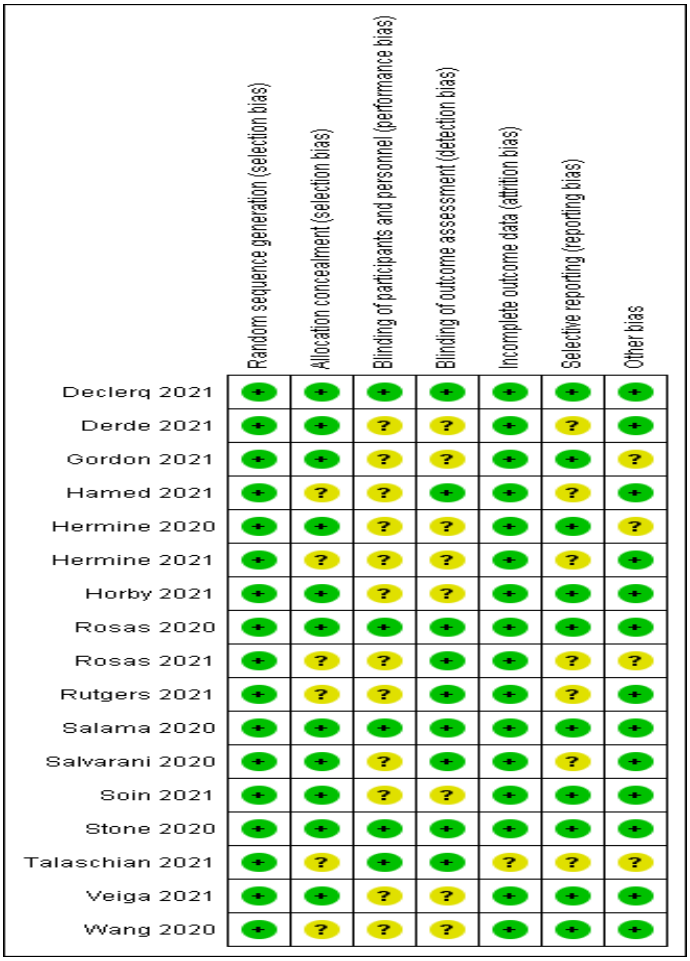
Salama 2020 N=388	Double-blind, placebo controlled RCT	USA, Mexico, Kenya, South Africa, Peru, Brazil	Hospitalized Covid-19 pneumonia patients n**ot** on continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation.	Tocilizumab 8mg/kg	Placebo	-Invasive mechanical ventilation or ECMO -Mortality -Time to hospital discharge or readiness for discharge -Time to at least a two-category improvement in clinical status -Time to clinical failure
Salvarani 2020 N=126	Open-label RCT	Italy	Non-ICU Covid-19 patients.	Tocilizumab 8mg/kg	Standard of care	-Clinical worsening at day 14 -Admission to ICU with mechanical ventilation -Death from any cause -PaO2/FIO2 ratio less than 150 mm Hg
Stone 2020 N=243	Double-blind, placebo controlled RCT	USA	Confirmed Covid-19 patients n**ot** on O2 above 10 L/minute	Tocilizumab 8mg/kg	Placebo	-Mortality -Mechanical ventilation -Clinical worsening -Time to improvement -Time to death -Duration of supplemental O2 -Admission to ICU
Wang 2020 N=65	Open-label RCT	China	Moderate or severe Covid-19 patients with elevated IL-6.	Tocilizumab	Standard of care	-Cure rate -Recovery rate of hypoxia over 14 days, -Worsening rate of hypoxia during hospitalization, -Duration of hospital stay, -Time to negative virus load.
Veiga 2021 N=129	Open-label RCT	Brazil	Severe or critical Covid-19 patients	Tocilizumab 8mg/kg	Standard of care	-Clinical status at Day 15 -All cause mortality -In-hospital mortality -Sequential organ failure assessment score -Clinical status at day 8 and day 29 -Ventilator-free days within 29 days -Time to independence from supplemental oxygen -Duration of hospital stay

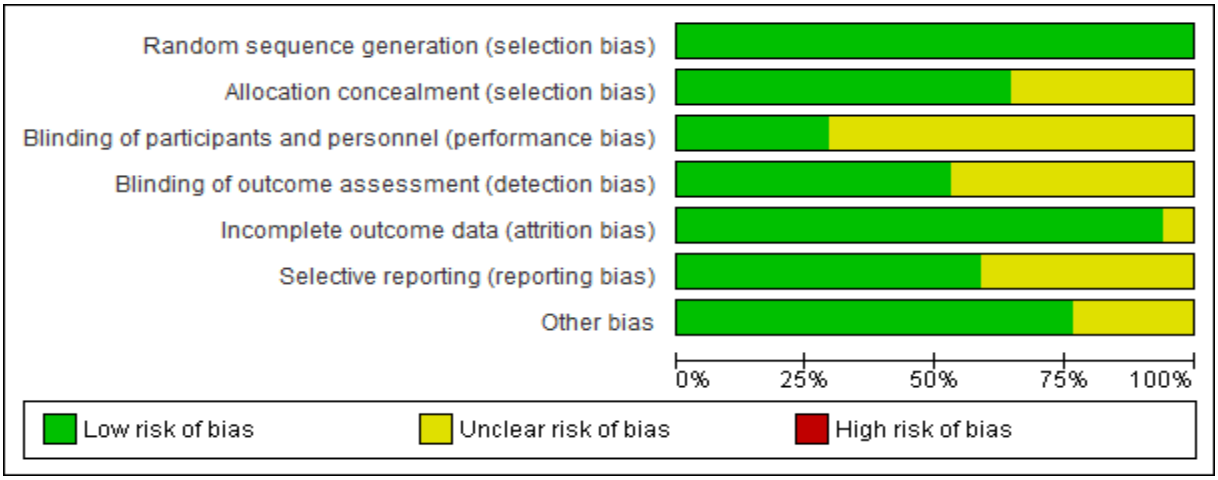
Soin 2021 (COVINTOC) N= 183	Open-label RCT	India	Moderate to severe Covid-19 patients Moderate – RR 15-30 AND SpO2 90-94% Severe- RR>30 OR SpO2 <90% OR ARDS OR septic shock	Tocilizumab 6 mg/ kg	Standard of care	-Clinical progression -Mortality -Clinical improvement -Time to clinical improvement -Ventilator free days -Organ failure-free days -ICU admission -Time to hospital discharge -Time to negative result on RT-PCR -Adverse events -Serious adverse events
Rutgers* 2021 N= 354	Open label RCT	The Netherlands	Hospitalized COVID 19 patients with the following conditions: Need for supplemental Oxygen Ferritin >2000 ug/l or doubling serum ferritin in 20-48 hours	Tocilizumab 8 mg/kg	Standard of care	-30-day mortality -Duration of hospital stay -ICU admission -Duration of ICU stay -Duration of mechanical ventilation -Time to mechanical ventilation -Time to death

Talaschian 2021 N= 40	Double blind RCT	Iran	COVID-19 patients with the following conditions: Elevated CRP (>10 mg/L)/ IL 6 (> 18 pg/ml) / Lymphopenia (WBC< 1100/MCL) O2 sat <93% or RR >24 Not connected to mechanical ventilator Not responding to standard COVID-19 treatment	Tocilizumab 8 mg/kg	Standard of care	-Clinical improvement -28-day mortality -Time to improvement
Derde 2021 N=2274	Open label, Adaptive RCT	US, Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK	ICU admitted critical Covid-19 patient AND receiving respiratory or cardiovascular organ support	Group 1: Tocilizumab 8 mg/kg Group 2: Sarilumab Group 3: Anakinra Group 4: Interferon B1a	Standard of care	-Respiratory and cardiovascular organ support-free days -Survival -In-hospital mortality 90 days -Time to ICU discharge -Time to hospital discharge
Hamed 2021 N=76	Open label RCT	Dubai	Hospitalized covid 19 patient AND Lung infiltrates >50% of lung fields within 48 hrs admission, O2 saturation <93% at rest on room air	Group 1: Methylprednisolone Group 2: Methylprednisolone and Tocilizumab	Historical control group	-All-cause mortality day 45 -Admission to ICU -Length of ICU stay -Invasive ventilation -Days on ventilation -Length of hospital stay

Hermine 2021 (CORIMUNO-TOCI-DEX) N= 453	Open label RCT	France	Moderate to severe COVID-19 requiring oxygen but without ventilation support, high flow or mech vent, WHO class 5	Tocilizumab 8mg/kg at Day 1 PLUS Dexamethasone 10mg/d for 5 days and tapering up to 10 days	Dexamethasone 10mg/d for 5 days and tapering up to 10 days	-Survival without mechanical ventilation at day 14 -WHO-CPS progression -Time to oxygen supply independency -Time to hospital discharge adverse events
Rosas 2021 (REMDECTA) N=649	Double blind RCT	Multicenter:Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA	included patients hospitalized with severe COVID-19 pneumonia requiring>6 L/min supplemental oxygen.	Tocilizumab 8 mg/kg + Remdesevir	Standard of care with Remdesevir only	-Time from randomization to hospital discharge or “ready for discharge” to day 28.
Declerq 2021 (COV-AID) N=153	Open label RCT	Multicenter: Belgium	-Older than 18 years -Laboratory proven diagnosis of COVID-19 with symptoms between 6 and 16 days -Ratio of the partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2; P:F ratio) of less than 350 mm Hg on room air or less than 280 mm Hg on supplemental oxygen and bilateral pulmonary infiltrates.	Tocilizumab 8 mg/kg	Standard of care	-Time to clinical improvement

Appendix 3A. Risk of Bias Summary





Appendix 3B. AGREE II Assessment

AGREE II

A critical group appraisal of: Philippine COVID-19 Living Clinical Practice Guidelines using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator:

Date: 18 January 2022

Email: pattiorduna@gmail.com

URL of this appraisal: http://www.agreetrust.org/group-appraisal/16554

Guideline URL: https://drive.google.com/file/d/1bRloJGUGOkcmK8PTiPo9P7iO7U3TLXbN/view?usp=sharing

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
89%	83%	88%	98%	85%	100%	83%	Yes - 1, Yes with modifications - 2, No - 0

Domain 1. Scope and Purpose			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 1	6	6	6
Item 2	5	7	7
Item 3	6	7	7

Domain 2. Stakeholder Involvement			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 4	6	6	6
Item 5	5	5	5
Item 6	7	7	7

Domain 3. Rigour of Development			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 7	6	6	6
Item 8	6	7	7
Item 9	6	7	7
Item 10	7	6	5
Item 11	6	7	7
Item 12	6	7	7
Item 13	5	5	5
Item 14	6	7	7

Domain 4. Clarity of Presentation			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 15	6	7	7
Item 16	7	7	7
Item 17	7	7	7

Domain 5. Applicability			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 18	7	7	7
Item 19	5	5	7
Item 20	5	5	6
Item 21	6	7	6

Domain 6. Editorial Independence			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 22	7	7	7
Item 23	7	7	7

Overall Assessment			
	Appraiser 2	Appraiser 4	Appraiser 3
OA1	6	6	6

Created online at www.agreetrust.org 18 January 2022

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Date: 18 January 2022

Email: pattiorduna@gmail.com

URL of this appraisal: http://www.agreetrust.org/group-appraisal/16554

Guideline URL:
https://drive.google.com/file/d/1bRIoJGUGOkcmK8PTiPo9P7iO7U3TLXbN/view?usp=sharing

Comments

Domain 1. Scope and Purpose

Item 1

- Appraiser 3: Benefits for local end-user and other stakeholders for the contextualized recommendations clearly and concisely written.
  Clearly state expected health benefits from the guideline for the patient population/society

Domain 2. Stakeholder Involvement

Item 4

- Appraiser 3: List the institution and geographical location (to show distribution within the Philippines) of the members of CPG development groups which will contribute to the aim of the CPG to contextualize the evidence to the local setting.

Item 5

- Appraiser 4: Representation of target population perspectives not clear
- Appraiser 3: Steering committee and in Consensus Panel composition it is not clearly stated who represented the patients\' perspective. Although it is stated that the members who had experienced COVID-19 could represent the patients. If patients\' perspective through literature review, clearly state this also in the methodology.

Domain 3. Rigour of Development

Item 7

- Appraiser 4: Comprehensive search strategy in summary. Individual search strategies for clinical specific clinical questions may not have been exhaustive (e.g. vitamin c) Appraiser 3: General
- descriptions are detailed and comprehensive. Show search strategy used per clinical question

Item 10

- Appraiser 4: Elaborate on voting process
- Appraiser 3: Provide description of the recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered and outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique.

Item 13

- Appraiser 4: Include other methods in external review such as rating or assessment scales from relevant stakeholders.

members of the webpage. The process/method of the external review (rating scale, open-ended questions) of DOH and PCHRD, number of reviewers, outcomes gathered (i.e. summary of findings) should also be described.

Domain 4. Clarity of Presentation

Item 17

- Appraiser 3: Key recommendations are tabulated. Also they are boxed for each clinical question.

Domain 5. Applicability

Item 19

- Appraiser 4: May provide more information on guideline application or implementation (e.g. algorithms)
- Appraiser 3: The CPG is a reference for the unified COVID-19 algorithms on testing and management which is published in the PSMID website.

Item 20

- Appraiser 4: Provide more detail on cost information and methods by which this was sought, relevance to recommendations
- Appraiser 3: Include health economist or PhilHealth representative in the SC or CP.

Item 21

- Appraiser 3: Results of CPG downloads were described as part of monitoring and auditing. Suggest to describe in more detail the process for auditing/monitoring and use of the guideline taking into consideration possible process measures, behavioral measures, clinical or health outcome measures.

Domain 6. Editorial Independence

Item 23

- Appraiser 3: Oversight committee to assess for COI of CPG group members is present.

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Appendix 4: GRADE Evidence Profile

Author(s): Jofermarie O. Pineda, MD; Maria Teresa S. Tolosa, MD, FPDS, DipCE; Ma. Lucila M. Perez, MD, MSc, FPPS
Question: Tocilizumab compared to Standard of Care for Children with Covid-19
Setting: Hospital
Bibliography: [1] Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384(16):1491-502.[2] Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021;384(16):1503-16.[3] Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;384(1):20-30.[4] Horby PWRCG. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-45.[5] Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2021;181(1):32-40.[6] Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2021;181(1):24-31.[7] Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020;383(24):2333-44.[8] Wang D, Fu B, Peng Z, Yang D, Han M, Li M, et al. Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. Front Med. 2021:1-9.[9] Veiga VC, Prats J, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ. 2021;372:n84[10] Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. 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. Lancet Respir Med. 2021;9(5):511-521 [11] Hamed DM, Belhoul KM, Al Maazmi NA, Ghayoor F, Moin M, Al Suwaidi M, et al. Intravenous methylprednisolone with or without tocilizumab in patients with severe COVID-19 pneumonia requiring oxygen support: A prospective comparison. Journal of Infection and Public Health. 2021; 9(8): 985-989[12] Declercq J, Van Damme KFA, De Leeuw E, et al. Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. Lancet Respir Med. 2021;9(12):1427-1438. doi:10.1016/S2213-2600(21)00377-5[13] Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med. 2021;47(11):1258-1270. doi:10.1007/s00134-021-06507-x[14] Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Simon TM, Porcher R, et al . Pre-print: Tocilizumab Plus Dexamethasone in Patients with Moderate-to-Severe COVID-19 Pneumonia: a Randomized Clinical Trial of the CORIMUNO-19 Study Group. 2021[15] Talaschian M, Akhtari M, Mahmoudi M, Mostafaei S, Jafary M, Husseini A, et al. Preprint: Tocilizumab Failed to Reduce Mortality in Severe COVID-19 Patients: Results From a Randomized Controlled Clinical Trial. Research Square. 2021.[16] Rutgers A, Westerweel P, van der Holt B, Simone Postma, van Vonderen MGA, Djura P. Piersma, et al. Preprint: Timely administration of tocilizumab improves survival of hospitalized COVID-19 patients. 2021.[17] Derde LP, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Pre-print: Effectiveness of Tocilizumab, Sarilumab, and Anakinra for critically ill patients with COVID-19 The REMAP-CAP COVID-19 Immune Modulation Therapy Domain Randomized Clinical Trial. 2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
All Cause Mortality (follow-up range 14 days to 90 days)												
16	randomised trials N=9,584	serious[a]	not serious	serious[b]	not serious	none	1321/5286 (25.0%)	1228/4298 (28.6%)	**RR 0.88** (0.82 to 0.94)	**34 fewer per 1,000** (from 51 fewer to 17 fewer)	⊕⊕◯◯ Low	CRITICAL
Mortality Outcome on Day 28												
13	randomised trials N=8,027	serious[a]	not serious	serious[b]	not serious	none	992/4236 (23.4%)	1064/3791 (28.1%)	**RR 0.87** (0.81 to 0.94)	**36 fewer per 1,000** (from 53 fewer to 17 fewer)	⊕⊕◯◯ Low	CRITICAL
Mortality Outcome on Day 90												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials N=2,526	serious[a]	not serious	serious[b]	serious[d]	none	383/1597 (24.0%)	214/929 (23.0%)	**RR 0.89** (0.78 to 1.03)	**25 fewer per 1,000** (from 51 fewer to 7 more)	⨁◯◯◯ Very low	CRITICAL
Clinical Improvement at Day 28												
8	randomised trials N=5,625	serious[a]	not serious	serious[b]	not serious	none	1778/2952 (60.2%)	1434/2673 (53.6%)	**RR 1.06** (0.99 to 1.12)	**32 more per 1,000** (from 5 fewer to 64 more)	⨁⨁◯◯ Low	CRITICAL
Need for Mechanical Ventilation												
9	randomised trials N=5,365	serious[a]	not serious	serious[b]	not serious	none	342/2741 (12.5%)	408/2624 (15.5%)	**RR 0.78** (0.68 to 0.89)	**34 fewer per 1,000** (from 50 fewer to 17 fewer)	⨁⨁◯◯ Low	CRITICAL
Length of Hospital Stay												
2	randomised trials N=182	serious[a]	not serious	serious[b]	serious[c]	none	91	91	-	MD **1.94 lower** (6.8 lower to 2.91 higher)	⨁◯◯◯ Very low	CRITICAL
Length of ICU Stay												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials N=670	serious[a]	not serious	serious[b]	serious[c]	none	411	259	-	MD **2.5 lower** (6.8 lower to 1.8 higher)	⊕◯◯◯ Very low	CRITICAL
Adverse Events												
9	randomised trials N=2,323	serious[a]	not serious	serious[b]	serious[c]	none	844/1447 (58.3%)	439/876 (50.1%)	**RR 1.03** (0.97 to 1.11)	**15 more per 1,000** (from 15 fewer to 55 more)	⊕◯◯◯ Very low	CRITICAL
Serious Adverse Event												
10	randomised trials N=2,532	serious[a]	not serious	serious[b]	serious[c]	none	241/1419 (17.0%)	164/1113 (14.7%)	**RR 0.92** (0.77 to 1.08)	**12 fewer per 1,000** (from 34 fewer to 12 more)	⊕◯◯◯ Very low	CRITICAL
Mortality Outcome when co-administered with steroids												
6	randomised trials N=4,407	serious[a]	not serious	serious[b]	not serious	none	534/2230 (23.9%)	664/2177 (30.5%)	**RR 0.80** (0.66 to 0.97)	**61 fewer per 1,000** (from 104 fewer to 9 fewer)	⊕⊕◯◯ Low	CRITICAL
Pooled effect of tocilizumab on mortality according to oxygen: Requiring Oxygen Supplementation												
8	randomised trials N=3,381	serious[a]	not serious	serious[b]	not serious	none	245/1807 (13.6%)	256/1574 (16.3%)	**RR 0.88** (0.75 to 1.04)	**20 fewer per 1,000** (from 41 fewer to 7 more)	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Pooled effect of tocilizumab on mortality according to oxygen: Requiring Non invasive Mechanical Ventilation												
2	randomised trials N=1,819	serious[a]	not serious	serious[b]	not serious	none	309/913 (33.8%)	358/906 (39.5%)	**RR 0.89** (0.79 to 1.00)	**43 fewer per 1,000** (from 83 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Pooled effect of tocilizumab on mortality according to oxygen: Requiring Invasive Mechanical Ventilation												
2	randomised trials N=730	serious[a]	not serious	serious[b]	serious[c]	none	145/381 (38.1%)	151/349 (43.3%)	**RR 0.97** (0.82 to 1.15)	**13 fewer per 1,000** (from 78 fewer to 65 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Some concerns with regards to the imbalance in the administration of antivirals and steroids as well as other supplemental medications. Other than this, some of the included studies have moderate risk of bias upon appraisal.
b. The population in all of the studies are adults.
c. Wide confidence interval with possibility for benefit and harm
d. Crosses 1

Appendix 5: Forest Plots

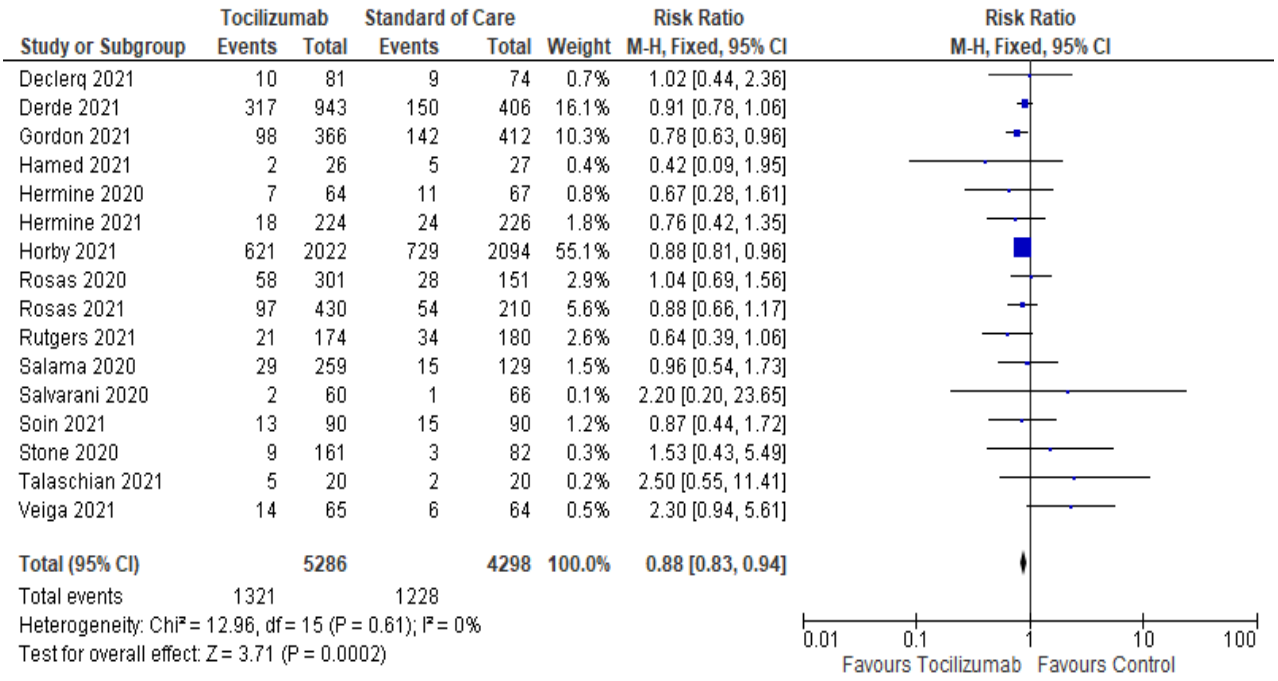

Figure 1. Pooled effect of Tocilizumab on all-cause mortality (d14 to d90)

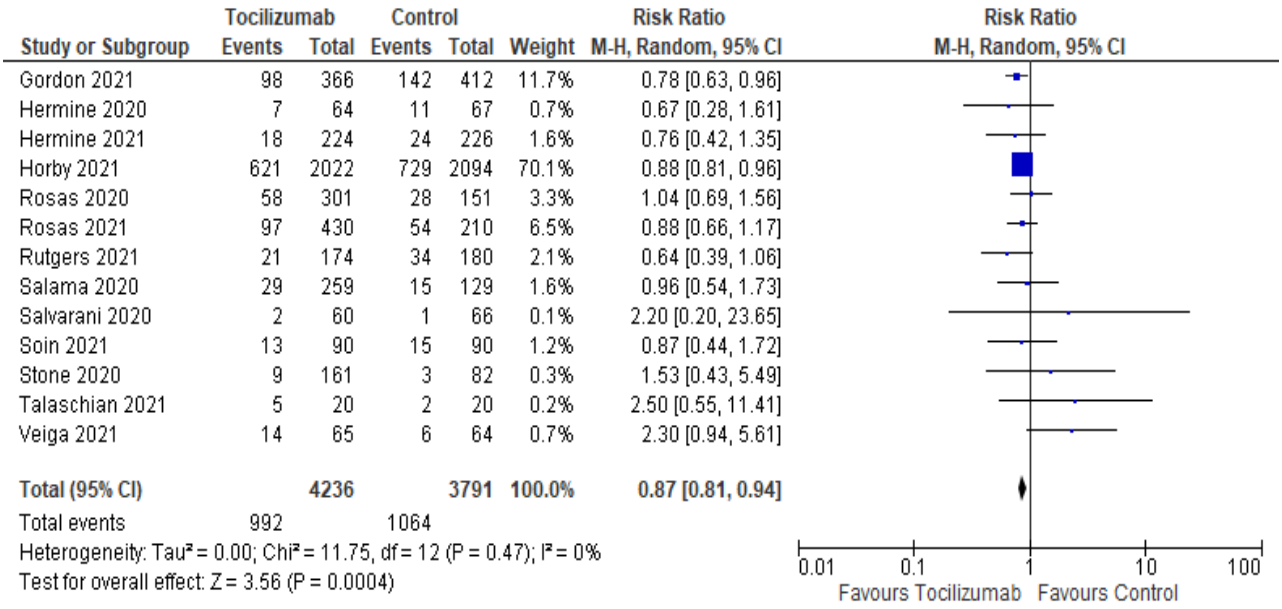

Figure 2. Mortality at 28 days

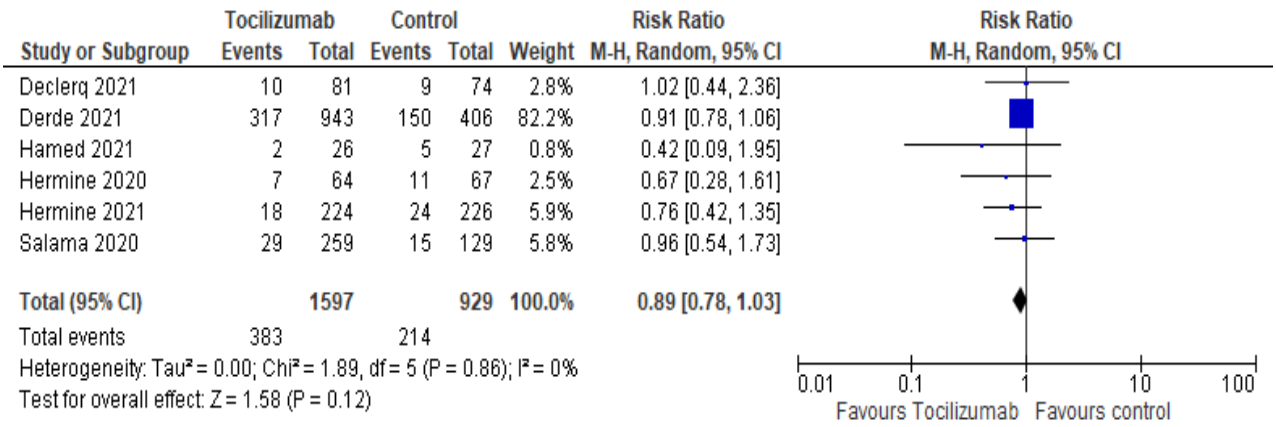

Figure 3. Mortality at 90days

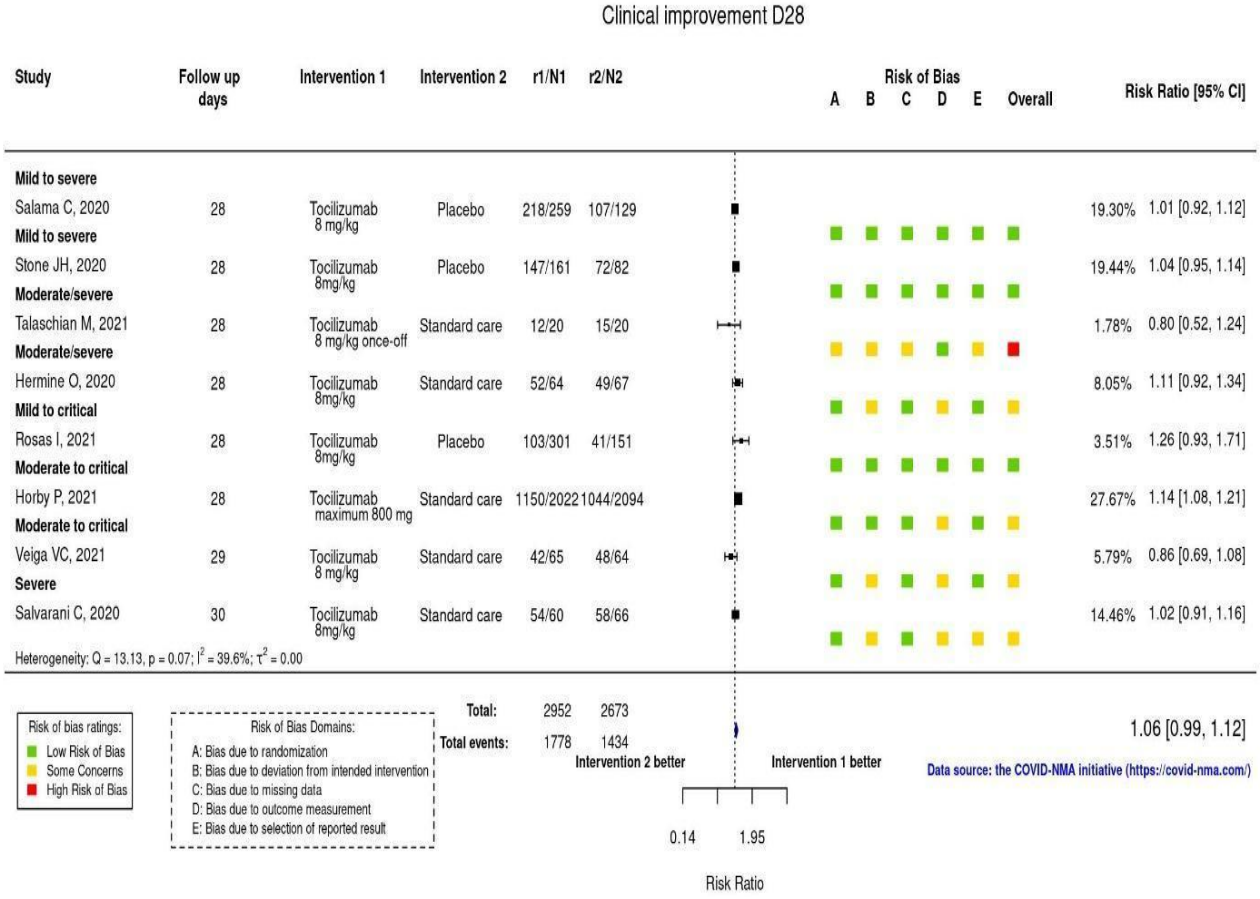

Figure 4. Clinical Improvement at 28days. Source: covid-nma.com

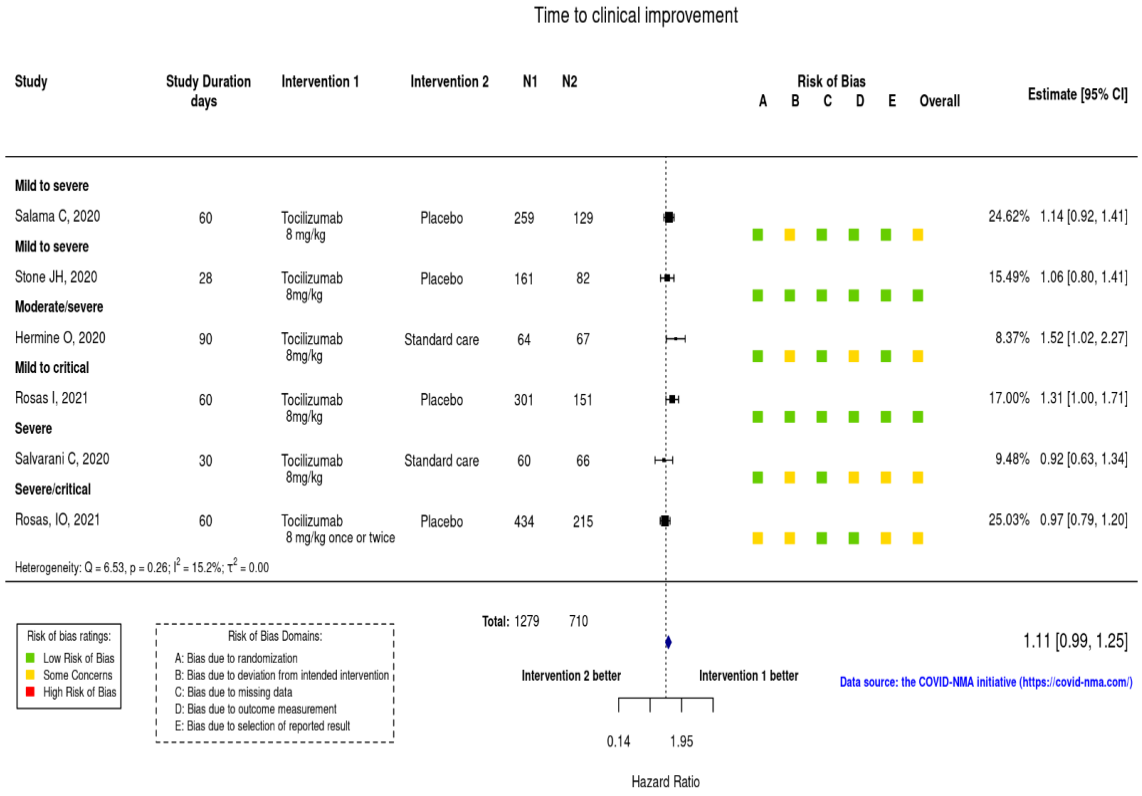

Figure 5. Effect of tocilizumab on time to clinical improvement (Hazard ratio). Source: covid-nma.com

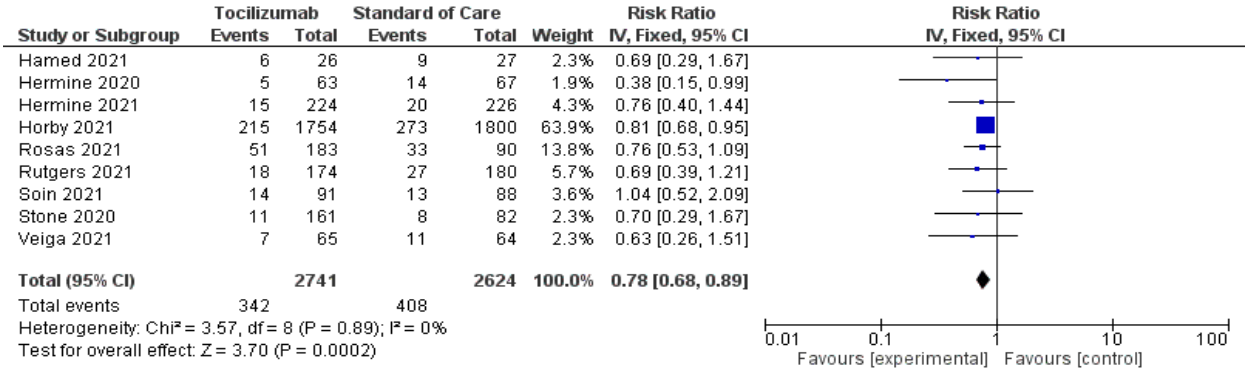

Figure 6. Pooled effect of tocilizumab on initiation of mechanical ventilation

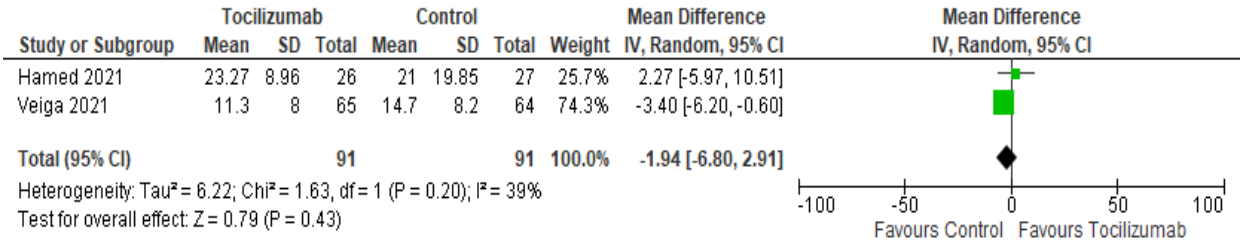

Figure 7. Length of Hospital Stay

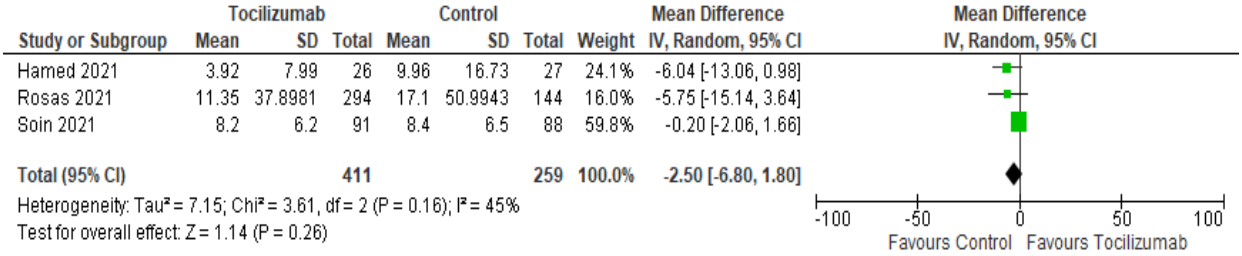

Figure 8. Length of ICU Stay

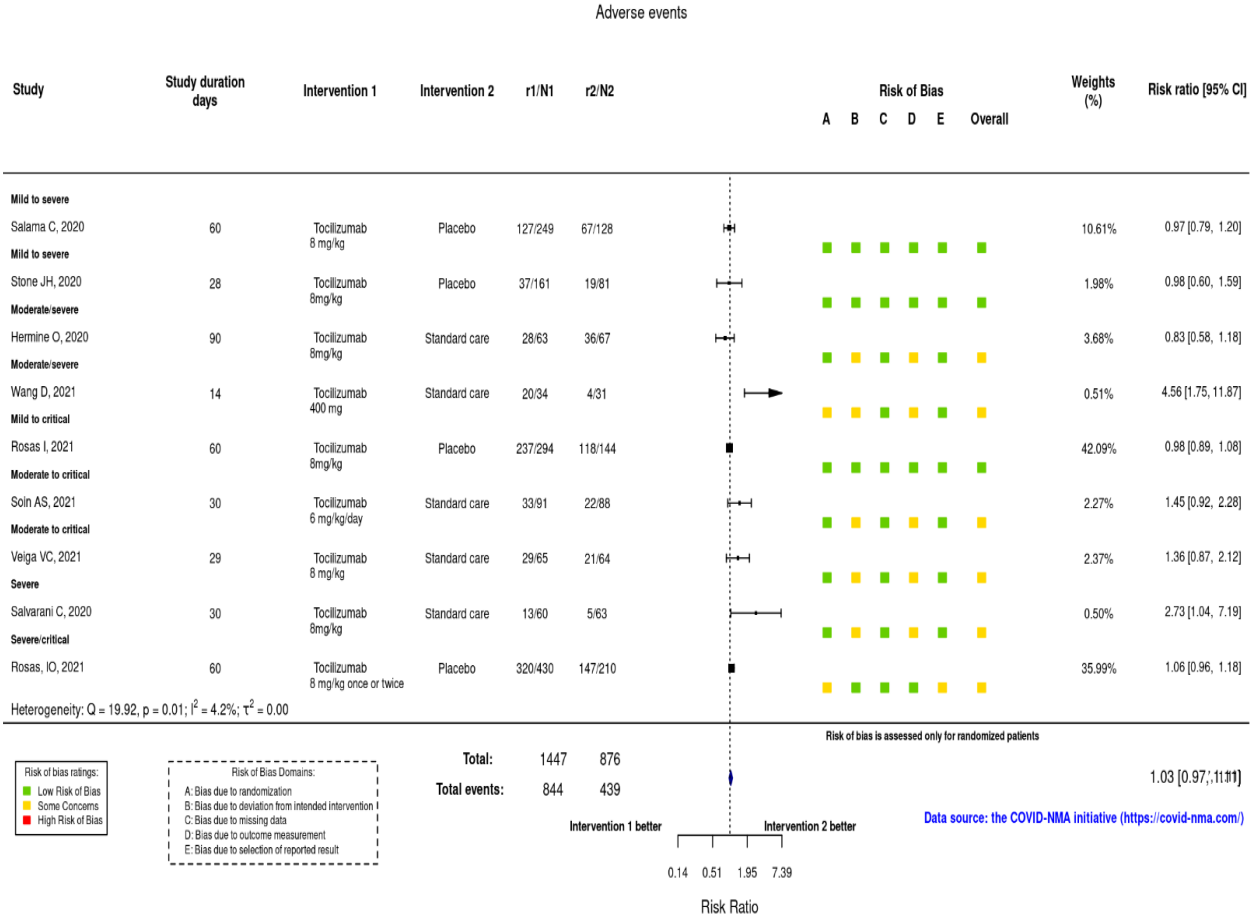

Figure 9. Pooled effect of tocilizumab on the incidence adverse event. Source: covid-nma.com

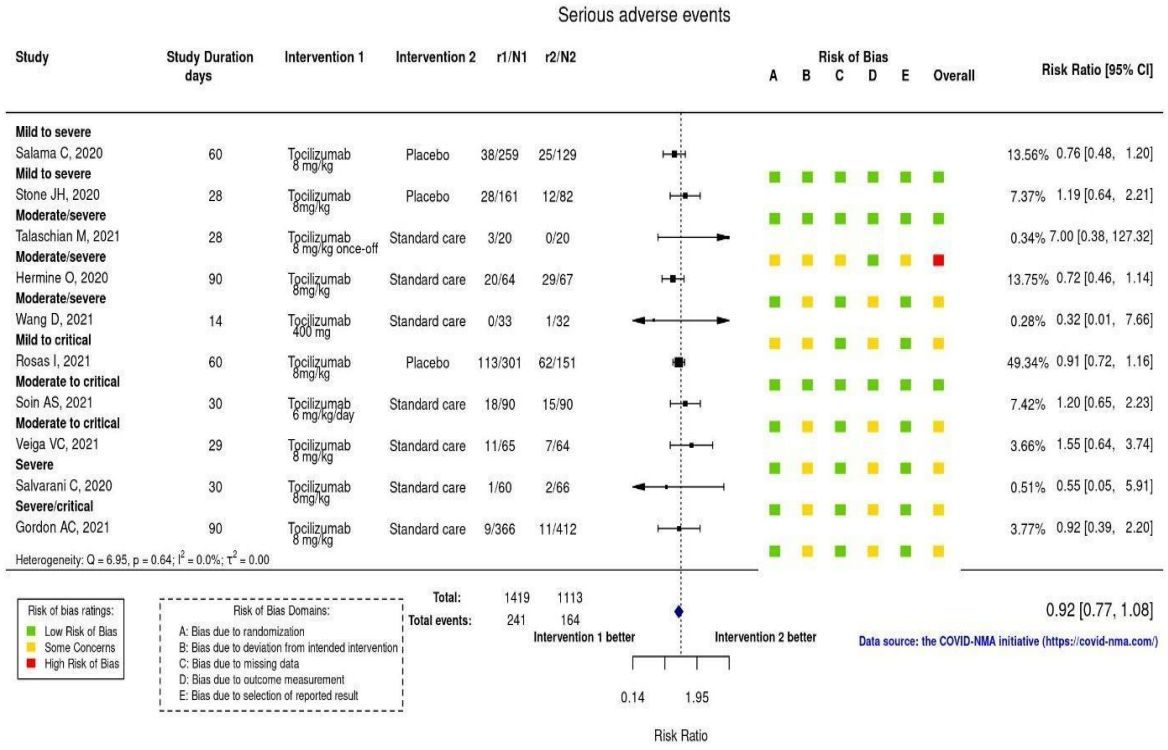

Figure 10. Pooled effect of tocilizumab on the incidence of serious adverse events. Source: covid-nma.com

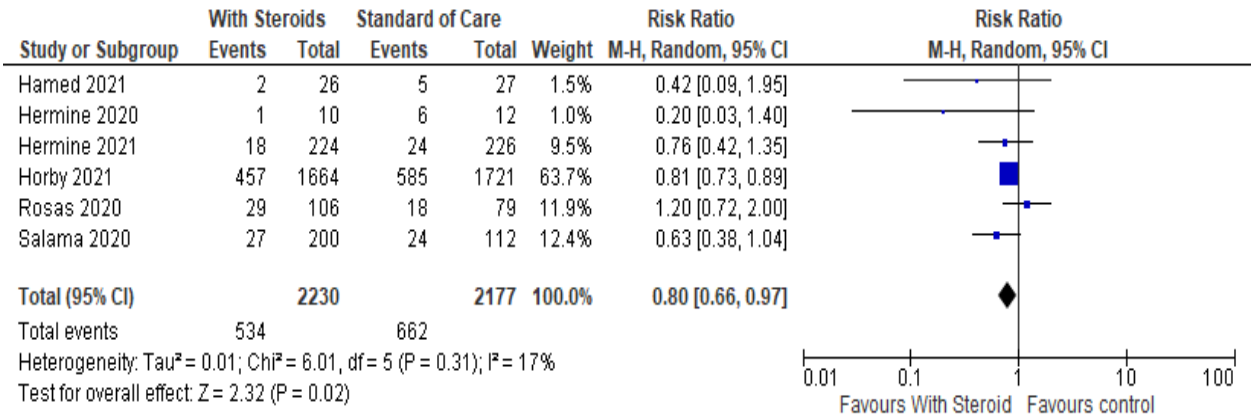

Figure 11. Pooled effect of tocilizumab on mortality with co-administration of steroids

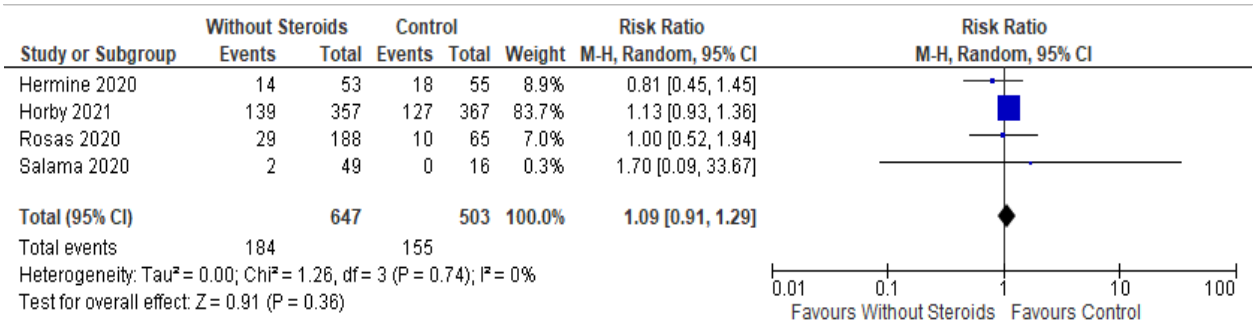

Figure 12. Pooled effect of tocilizumab on mortality without co-administration of steroids

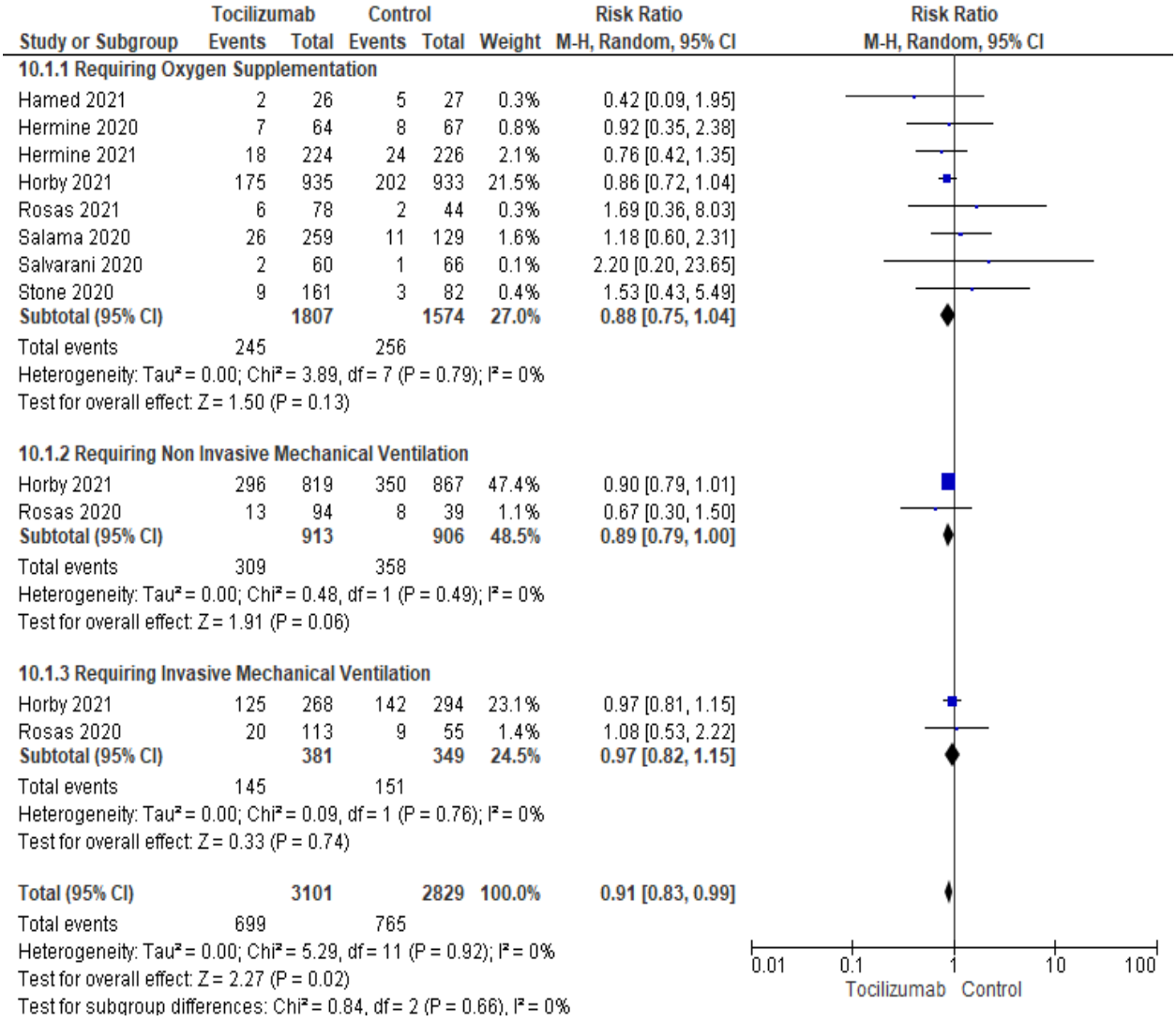

Figure 13. Pooled effect of tocilizumab on mortality according to oxygen requirement

Appendix 6: Characteristics of Ongoing Studies

Title/Identifier Expected Completion Date	Study Desig	Interventions	Patients/Population Recruited	Outcomes
NCT05164133 A Study Evaluating Tocilizumab in Pediatric Patients with Covid 19 Recruiting <u>Study Start:</u> January 15, 2022 <u>Completion date:</u> January 2, 2023	•Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Intervention: Tocilizumab Control: Standard of Care	-Up to 17 years old -With COVID-19 disease	•Serum concentration of TCZ •Maximum serum concentration (C max) of TCZ •Area under the curve from Days 0-28 (AUC days 0-28) of TCZ •Serum concentration on Day 28 (C day 28) of TCZ •Clearance (CL) of TCZ •Volume of distribution of TCZ •Duration of 90% saturation of sIL-6R •Concentration of IL-6 •Concentration of sIL-6R •Concentration of C-reactive protein •Percentage of participants with adverse events •Percentage of participants with severe adverse events

Appendix 7: Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS	JUDGEMENT (N = 11)							RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (11)		Varies		Uncertain		
Benefits	Large (1)	Moderate (10)	Small (1)	Trivial	Varies (1)	Uncertain		• Reduces all-cause mortality
Harm	Large	Moderate	Small (9)	Trivial (2)	Varies	Uncertain		• No significant different in adverse events and serious adverse events between intervention and control groups
Certainty of evidence	High	Moderate		Low (1)		Very low (10)		• Rated very low due to serious risk of bias, indirectness and imprecision
Balance of effects	Favors drug (3)	Probably favors drug (8)	Does not favor drug or no drug	Probably favors no drug	Favors no drug	Varies	Uncertain	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)		Probably no important uncertainty or variability (5)		No important uncertainty or variability		
Resources required	Uncertain	Varies	Large costs (11)	Moderate costs	Negligible costs or savings	Moderate savings	Large savings	• Php 28,830.84 per patient for retail price of 400mg/20mL vial
Certainty of evidence of resources required	No included studies (2)		Very low	Low	Moderate (8)	High (1)		
Cost-effectiveness	No included studies (1)	Varies	Favors the comparison (1)	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention (6)	Favors the intervention (3)	• Tocilizumab in combination with dexamethasone in adults was shown to be cost-effective in reducing COVID-related deaths in the severely ill.
Equity	Uncertain (4)	Varies (1)	Reduced (2)	Probably reduced (1)	Probably no impact	Probably increased (3)	Increased	
Acceptability	Uncertain (4)	Varies	No (1)	Probably no	Probably yes (6)	Yes (1)		
Feasibility	Uncertain (5)	Varies (1)	No	Probably no	Probably yes (3)	Yes (2)		

Additional Comments

- Because of the cost of the drug, accessibility and affordability may be a concern.