

In cooperation with the Pediatric Infectious Disease Society of the Philippines Funded by the Philippine Pediatric Society

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:

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

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

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	RESULTS		
		SEARCH	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 serological testing" [All Fields] OR "covid 19 serological testing" [All Fields] 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] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields] OR ("child" [MeSH Terms] OR "child" [All Fields] OR "children"[All Fields] OR "child s" [All Fields] OR "childrens"[All Fields] OR "childs" [All Fields] OR	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 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"s"[All Fields] OR "children's"[All Fields] OR "child's"[All Fields] OR "childs"[All Fields] OR	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	01/01/22	96	2
	With or without Children or Pediatrics	7:30PM		
	*For ongoing studies			
Chinese Clinical Trial	COVID Tocilizumab	01/01/22	3	0
Registry		8:00AM		
EU Clinical Trials	COVID Tocilizumab	01/01/22	6	4
Register		10:32AM		
Japan Primary	COVID Tocilizumab	01/01/22	0	0
Registries Network/ NIPH Clinical Trials Search		2:30PM		
chinaxiv.org	COVID Tocilizumab	01/01/22	1	0
		9:45AM		
Medrxiv.org	COVID Tocilizumab	01/01/22	5	5
		11:50AM		
Biorxiv.org	COVID Tocilizumab	01/01/22	0	0
		12:42PM		



Appendix 2. Characteristics of Included Studies

Title/Author	Study design	Country	Population	Intervention Group(s)	Control	Outcomes
Horby 2021 RECOVERY	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
N=4116						-Time to successful cessation of invasive mechanical ventilation -Use of renal dialysis/hemofiltration -Major cardiac arrhythmia -Serious adverse events
Gordon 2020 REMAP-CAP	Adaptive RCT	Multicenter; United Kingdom,	ICU admitted critical Covid-19 patients AND	Group 1: Tocilizumab 8 mg/kg	Standard of care	-Respiratory and cardiovascular organ support-free days -Survival -Time to ICU discharge
N=755		France, the Netherlands, Australia	receiving respiratory or cardiovascular organ support	Group 2: Sarilumab		-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	Double-blind, placebo controlled	Canada, Denmark, France,	Severe Covid-19 patients	Tocilizumab 8mg/kg	Placebo	-Clinical status at day 28 -Mortality -Ventilator free days
N=452	RCT	Germany, Italy, Netherland,Sp ain, UK, USA				-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	Open-label	India	Moderate to	Tocilizumab	Standard	-Clinical progression
(COVINTOC)	RCT	india	severe	6 mg/ kg	of care	-Mortality
(00111100)			Covid-19 patients	o mg/ ng	or our o	-Clinical improvement
N= 183						-Time to clinical improvement
			Moderate – RR			-Ventilator free days
			15-30 AND			-Organ failure-free days
			SpO2 90-94%			-ICU admission
						-Time to hospital discharge
			Severe-			-Time to negative result on RT-PCR
			RR>30 OR			-Adverse events
			SpO2 <90% OR			-Serious adverse events
			ARDS OR septic			
			shock			
Rutgers* 2021	Open label	The	Hospitalized	Tocilizumab	Standard	-30-day mortality
	RCT	Netherlands	COVID 19 patients	8 mg/kg	of care	-Duration of hospital stay
N= 354			with the following			-ICU admission
			conditions:			-Duration of ICU stay
						-Duration of mechanical ventilation
			Need for			-Time to mechanical ventilation
			supplemental			-Time to death
			Oxygen			
			Ferritin >2000 ug/l			
			or doubling serum ferritin in 20-48			
			hours			



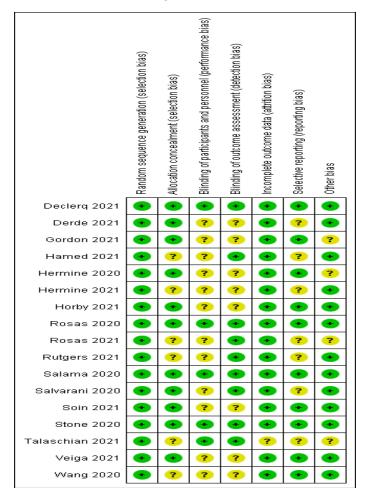
Talaschian 2021 N= 40 Derde	Double blind RCT	Iran US, Australia,	COVID-19 patients with the following conditions: Elevated CRP (>10 mg/L)/ IL 6 (> 18 pg/ml) / Lymphopenia (WBC< 1100/MCL) O2 sat <93% or RR >24 Not connected to mechanical ventilator Not responding to standard COVID- 19 treatment ICU admitted	Tocilizumab 8 mg/kg Group 1:	Standard of care	-Clinical improvement -28-day mortality -Time to improvement -Time to improvement
2021 N=2274	Adaptive RCT	Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK	critical Covid-19 patient AND receiving respiratory or cardiovascular organ support	Tocilizumab 8 mg/kg Group 2: Sarilumab Group 3: Anakinra Group 4: Interferon B1a	of care	-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

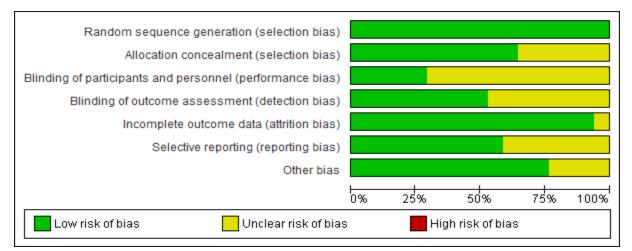


Hermine 2021 (CORIMUNO- TOCI-DEX) N= 453	Open label RCT	France	Moderate to severe COVID-19 requiring oxygen but without ventilation support, high flow or mech vent, WHO class 5	Tocilizumab 8mg/kg at Day 1 PLUS Dexamethasone 10mg/d for 5 days and tapering up to 10 days	Dexameth asone 10mg/d for 5 days 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:Ca nada, 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 Remdesev ir 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



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/1bRioJGUGOkcmK8PTiPo9P7iO7U3TLXbN/view?usp=sharin.g

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	Appraiser 2	Appraiser 4	Appraiser 3
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ltem 23	7	7	7
Overall A	ssessment		
	Appraiser 2	Appraiser 4	Appraiser 3

Created online at www.agreetrust.org 18 January 2022





AGREEII

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=sharin.g

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 (<u>e.g.</u> 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 (<u>i.e.</u> summary of findings) should also be described.

Domain 4. Clarity of Presentation

ltem 17

 Appraiser 3: Key recommendations are tabulated. <u>Also</u> they are boxed for each clinical question.

Domain 5. Applicability

ltem 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 III 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;1-9,191 Veica VC, Prats J, Farias DLC, Rosa RG, Dourado LK, Zamoieri 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); 985-989/121 Declercg J. Van Damme KFA. De Leeuw E. et al. Effect of anti-interleukin druos 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, and Anakinra for critically ill patients with COVID-19 The REMAP-CAP COVID-19 Immune Modulation Therapy Domain Randomized Clinical Trial. 2021

		Ce	rtainty assessmen	t			Nº of patients Effect		fect	Certainty	Importance	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% Cl)	Absolute (95% Cl)	Gertainty	
All Cause Mortali	ty (follow-up range 14 day	s to 90 days)										
16	randomised trials	seriousª	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	⊕⊕⊖⊖ Low	CRITICAL
	N=9,584									fewer)		
Mortality Outcom	e on Day 28											
13	randomised trials	seriousª	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	⊕⊕⊖⊖ Low	CRITICAL
	N=8,027									fewer)		
Mortality Outcom	e on Day 90											



		Ce	rtainty assessmen	t			№ of patients			Effect		Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
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
linical Improven	nent at Day 28											
8	randomised trials N=5,625	seriousª	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
leed for Mechani	cal Ventilation									I		
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
9 _ength of Hospita	N=5,365	serious ^a	not serious	serious ^b	not serious	none			(0.68 to	per 1,000 (from 50 fewer to 17		CRITICAL
	N=5,365	serious ^a	not serious	serious ^b	not serious	none			(0.68 to	per 1,000 (from 50 fewer to 17		CRITICAL



		Ce	rtainty assessmen	t			Nº of pa	atients	Ef	fect	Outsists	Inconstants
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
3	randomised trials N=670	seriousª	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		1							•	•		
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	seriousª	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 Outcom	e when co-administered w	vith steroids										
6	randomised trials N=4,407	seriousª	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 to	ocilizumab on mortality ac	cording to oxyg	en: Requiring Ox	ygen Supplementa	tion	<u> </u>	<u> </u>	<u> </u>	<u> </u>	<u> </u>	<u> </u>	
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



		Ce	rtainty assessmen	t			№ of pa	atients	Ef	ffect	Containty	luun outon oo
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% Cl)	Absolute (95% Cl)	Certainty	Importance
Pooled effect of to	ocilizumab on mortality ac	cording to oxyg	en: Requiring No	n invasive Mechan	ical Ventilation							
2	randomised trials N=1,819	seriousª	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 to	ocilizumab on mortality ac	cording to oxyg	en: Requiring Inv	asive Mechanical V	Ventilation							
2	randomised trials N=730	seriousª	not serious	serious ^b	serious°	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

	Tocilizu	mab	Standard of	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Declerq 2021	10	81	9	74	0.7%	1.02 [0.44, 2.36]	
Derde 2021	317	943	150	406	16.1%	0.91 [0.78, 1.06]	+
Gordon 2021	98	366	142	412	10.3%	0.78 [0.63, 0.96]	-
Hamed 2021	2	26	5	27	0.4%	0.42 [0.09, 1.95]	
Hermine 2020	7	64	11	67	0.8%	0.67 [0.28, 1.61]	
Hermine 2021	18	224	24	226	1.8%	0.76 [0.42, 1.35]	
Horby 2021	621	2022	729	2094	55.1%	0.88 [0.81, 0.96]	
Rosas 2020	58	301	28	151	2.9%	1.04 [0.69, 1.56]	
Rosas 2021	97	430	54	210	5.6%	0.88 [0.66, 1.17]	
Rutgers 2021	21	174	34	180	2.6%	0.64 [0.39, 1.06]	
Salama 2020	29	259	15	129	1.5%	0.96 [0.54, 1.73]	
Salvarani 2020	2	60	1	66	0.1%	2.20 [0.20, 23.65]	
Soin 2021	13	90	15	90	1.2%	0.87 [0.44, 1.72]	
Stone 2020	9	161	3	82	0.3%	1.53 [0.43, 5.49]	
Talaschian 2021	5	20	2	20	0.2%	2.50 [0.55, 11.41]	
Veiga 2021	14	65	6	64	0.5%	2.30 [0.94, 5.61]	
Total (95% CI)		5286		4298	100.0%	0.88 [0.83, 0.94]	•
Total events	1321		1228				
Heterogeneity: Chi ² =	12.96, df =	= 15 (P :	= 0.61); I ² = 09	5			0.01 0.1 1 10 100
Test for overall effect:	Z= 3.71 (P = 0.00)02)				0.01 0.1 1 1 10 100 Favours Tocilizumab Favours Control
			•				Favours rocilizumab Favours Control

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

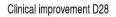
	Tocilizu	mab	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Gordon 2021	98	366	142	412	11.7%	0.78 [0.63, 0.96]	-
Hermine 2020	7	64	11	67	0.7%	0.67 [0.28, 1.61]	
Hermine 2021	18	224	24	226	1.6%	0.76 [0.42, 1.35]	
Horby 2021	621	2022	729	2094	70.1%	0.88 [0.81, 0.96]	
Rosas 2020	58	301	28	151	3.3%	1.04 [0.69, 1.56]	+
Rosas 2021	97	430	54	210	6.5%	0.88 [0.66, 1.17]	
Rutgers 2021	21	174	34	180	2.1%	0.64 [0.39, 1.06]	
Salama 2020	29	259	15	129	1.6%	0.96 [0.54, 1.73]	_
Salvarani 2020	2	60	1	66	0.1%	2.20 [0.20, 23.65]	
Soin 2021	13	90	15	90	1.2%	0.87 [0.44, 1.72]	
Stone 2020	9	161	3	82	0.3%	1.53 [0.43, 5.49]	
Talaschian 2021	5	20	2	20	0.2%	2.50 [0.55, 11.41]	
Veiga 2021	14	65	6	64	0.7%	2.30 [0.94, 5.61]	
Total (95% CI)		4236		3791	100.0%	0.87 [0.81, 0.94]	•
Total events	992		1064				
Heterogeneity: Tau ² =	0.00; Chi	² = 11.7	5, df = 12	(P = 0)	47); l² = 0	%	
Test for overall effect:	Z = 3.56 (P = 0.00)04)				0.01 0.1 1 10 100 Favours Tocilizumab Favours Control

Figure 2. Mortality at 28 days



	Tocilizu	mab	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Declerq 2021	10	81	9	74	2.8%	1.02 [0.44, 2.36]	
Derde 2021	317	943	150	406	82.2%	0.91 [0.78, 1.06]	
Hamed 2021	2	26	5	27	0.8%	0.42 [0.09, 1.95]	
Hermine 2020	7	64	11	67	2.5%	0.67 [0.28, 1.61]	
Hermine 2021	18	224	24	226	5.9%	0.76 [0.42, 1.35]	-+-
Salama 2020	29	259	15	129	5.8%	0.96 [0.54, 1.73]	
Total (95% CI)		1597		929	100.0%	0.89 [0.78, 1.03]	•
Total events	383		214				
Heterogeneity: Tau ² =	= 0.00; Chř	² = 1.89	, df = 5 (F	, = 0.86); I ^z = 0%		
Test for overall effect	: Z = 1.58 (P = 0.12	2)				0.01 0.1 1 10 10 Favours Tocilizumab Favours control

Figure 3. Mortality at 90days



Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2		A	В	Risk o C	of Bias D	E	Overall	Risk Ratio [95% Cl]
										_		
28	Tocilizumab	Placebo	218/259	107/129	i.							19.30% 1.01 [0.92, 1.12]
	8 mg/kg											
28	Tocilizumab	Placebo	147/161	72/82	i i							19.44% 1.04 [0.95, 1.14]
	8mg/kg											
28	Tocilizumab	Standard care	12/20	15/20	ц.							1.78% 0.80 [0.52, 1.24]
	8 mg/kg once-off											
28	Tocilizumab	Standard care	52/64	49/67								8.05% 1.11 [0.92, 1.34]
	8mg/kg											
28	Tocilizumab	Placebo	103/301	41/151	÷.							3.51% 1.26 [0.93, 1.71]
	8mg/kg											
28	Tocilizumab	Standard care	1150/2022	1044/2094								27.67% 1.14 [1.08, 1.21]
	maximum 800 mg											
29	Tocilizumab	Standard care	42/65	48/64	Hei							5,79% 0.86 [0.69, 1.08]
	8 mg/kg											
30	Tocilizumab 8mg/kg	Standard care	54/60	58/66	•			-		ŝ		14.46% 1.02 [0.91, 1.16]
= 0.07; $ ^2$ = 39.6%; τ^2	= 0.00									2	12	
A: Bias due to ra B: Bias due to de C: Bias due to m D: Bias due to ou	undomization aviation from intended interven iissing data utcome measurement			Г		rvention 1	better		Data s	ource:	the COVID-NM	1.06 [0.99, 1.12] A initiative (https://covid-nma.com/
	days 28 28 28 28 28 28 28 28 28 28	days 28 Tocilizumab 8 mg/kg 28 Tocilizumab 8mg/kg 28 Tocilizumab 8 mg/kg 29 Tocilizumab 8 mg/kg 30 Tocilizumab 8 mg/kg 4: Bias due to randomization	days 28 Tocilizumab 8 mg/kg Placebo 28 Tocilizumab 8 mg/kg Placebo 28 Tocilizumab 8 mg/kg Placebo 28 Tocilizumab 8 mg/kg Standard care 28 Tocilizumab 8 mg/kg Standard care 28 Tocilizumab 8 mg/kg Placebo 28 Tocilizumab 8 mg/kg Standard care 29 Tocilizumab 8 mg/kg Standard care 30 Tocilizumab 8 mg/kg Standard care 30 Tocilizumab 8 mg/kg Standard care 30 Tocilizumab 8 mg/kg Standard care 1 Flisk of Bias Domains: A: Bias due to andomization B: Bias due to outcome measurement Total events: Total events:	days 28 Tocilizumab 8 mg/kg Placebo 218/259 28 Tocilizumab 8 mg/kg Placebo 147/161 28 Tocilizumab 8 mg/kg Placebo 147/161 28 Tocilizumab 8 mg/kg Standard care 12/20 28 Tocilizumab 8 mg/kg Standard care 52/64 28 Tocilizumab 8 mg/kg Placebo 103/301 28 Tocilizumab 8 mg/kg Standard care 1150/2022 29 Tocilizumab 8 mg/kg Standard care 42/65 30 Tocilizumab 8 mg/kg Standard care 54/60 30 Tocilizumab 8 mg/kg Standard care 54/60 1 Tocilizumab 8 mg/kg Standard care 54/60 29 Tocilizumab 8 mg/kg Standard care 54/60 1 Tocilizumab 8 mg/kg Standard care 54/60 1 Tocilizumab 8 mg/kg Standard care 54/60 1 Total 2952 100	days 28 Tocilizumab 8 mg/kg Placebo 218/259 107/129 28 Tocilizumab 8 mg/kg Placebo 147/161 72/82 28 Tocilizumab 8 mg/kg Placebo 147/161 72/82 28 Tocilizumab 8 mg/kg Standard care 12/20 15/20 28 Tocilizumab 8 mg/kg Standard care 52/64 49/67 28 Tocilizumab 8 mg/kg Placebo 103/301 41/151 28 Tocilizumab 9 mg/kg Standard care 1150/20221044/2094 29 Tocilizumab 8 mg/kg Standard care 42/65 48/64 30 Tocilizumab 8 mg/kg Standard care 54/60 58/66 1= 0.07; I ² = 39.6%; τ ² = 0.00 Total events: 1778 1434 Total events: 1778 1434 Intervention 2 better C: Bas due to deviation from intended intervention Total events: 1778 1434 D: Bias due to missing data Total events 1778 1434	days 28 Tocilizumab 8 mg/kg Placebo 218/259 107/129 28 Tocilizumab 8 mg/kg Placebo 147/161 72/82 28 Tocilizumab 8 mg/kg Standard care 12/20 15/20 28 Tocilizumab 8 mg/kg Standard care 52/64 49/67 28 Tocilizumab 8 mg/kg Placebo 103/301 41/151 28 Tocilizumab 8 mg/kg Placebo 103/301 41/151 28 Tocilizumab 8 mg/kg Standard care 1150/20221044/2094 • 28 Tocilizumab 8 mg/kg Standard care 42/65 48/64 • 29 Tocilizumab 8 mg/kg Standard care 54/60 58/66 • 30 Tocilizumab 8 mg/kg Standard care 54/60 58/66 • 1= 0.07; I ² = 39.6%; τ ² = 0.00 Total 292 2673 • 10 Bias due to deviation from intended intervention C: Bas due to missing data 1778 1434 • 10 Bas due to missing data • • • • 10 Bas	days A 28 Tocilizumab 8 mg/kg Placebo 218/259 107/129 • 28 Tocilizumab 8 mg/kg Placebo 147/161 72/82 • 28 Tocilizumab 8 mg/kg once-off Standard care 12/20 15/20 • 28 Tocilizumab 8 mg/kg Standard care 52/64 49/67 • 28 Tocilizumab 8 mg/kg Placebo 103/301 41/151 • 28 Tocilizumab 8 mg/kg Placebo 103/301 41/151 • 28 Tocilizumab 8 mg/kg Standard care 1150/20221044/2094 • 29 Tocilizumab 8 mg/kg Standard care 42/65 48/64 • 30 Tocilizumab 8 mg/kg Standard care 54/60 58/66 • *= 0.07; I* = 39.6%; rt ² = 0.00 Total events: 1778 1434 •	days A B 28 Tocilizumab 8 mg/kg Placebo 218/259 107/129 •	days A B C 28 Tocilizumab 8 mg/kg Placebo 218/259 107/129 28 Tocilizumab 8 mg/kg Placebo 147/161 72/82 28 Tocilizumab 8 mg/kg Standard care 12/20 15/20 28 Tocilizumab 8 mg/kg Standard care 52/64 49/67 28 Tocilizumab 8 mg/kg Standard care 52/64 49/67 28 Tocilizumab 8 mg/kg Standard care 150/20221044/2094 4 28 Tocilizumab 8 mg/kg Standard care 42/65 48/64 29 Tocilizumab 8 mg/kg Standard care 54/60 58/66 30 Tocilizumab 8 mg/kg Standard care 54/60 58/66 4 Bias due to anomization B Bias due to advision from interded intervention C Bas due to advision	days A B C D 28 Tocilizumab 8mg/kg Placebo 218/259 107/129 •<	days A B C D E 28 Tocilizumab 8mg/kg Placebo 218/259 107/129 •<	days A B C D E Overall 28 Tocilizumab 8mg/kg Placebo 218/259 107/129 •

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



				Tir	me to clin	ical improvement						
Study	Study Duration days	Intervention 1	Intervention 2	N1	N2		A	Risk (B (of Bias C D	E	Overall	Estimate [95% CI]
Mild to severe												
Salama C, 2020	60	Tocilizumab	Placebo	259	129	•	_		_			24.62% 1.14 [0.92, 1.41]
Mild to severe		8 mg/kg									•	
Stone JH, 2020	28	Tocilizumab	Placebo	161	82	H H H	_	_	_	_	_	15.49% 1.06 [0.80, 1.41]
Moderate/severe		8mg/kg									•	
Hermine O, 2020	90	Tocilizumab	Standard care	64	67	ļ.	_		_		_	8.37% 1.52 [1.02, 2.27]
Mild to critical		8mg/kg							-		•	
Rosas I, 2021	60	Tocilizumab	Placebo	301	151		_		_	_	_	17.00% 1.31 [1.00, 1.71]
Severe		8mg/kg									•	
Salvarani C, 2020	30	Tocilizumab	Standard care	60	66	H=1		_	_	_	_	9.48% 0.92 [0.63, 1.34]
Severe/critical		8mg/kg									•	
Rosas, IO, 2021	60	Tocilizumab 8 mg/kg once or twice	Placebo	434	215	•					•	25.03% 0.97 [0.79, 1.20]
Heterogeneity: Q = 6.53, p	= 0.26; I^2 = 15.2%; τ^2 = 0.0	0										
Risk of bias ratings: Low Risk of Bias Some Concerns High Risk of Bias	A: Bias due to rando	ion from intended intervention ng data me measurement	To	tal: 1279 Interv	710 rention 2 bette 0.	r Interven	ation 1 bet	ter	Data se	ource: t	the COVID-NMA	1.11 [0.99, 1.25] initiative (https://covid-nma.com/)
						Hazard Ratio						

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

	Tocilizu	mab	Standard of	Care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
Hamed 2021	6	26	9	27	2.3%	0.69 [0.29, 1.67]	
Hermine 2020	5	63	14	67	1.9%	0.38 [0.15, 0.99]	
Hermine 2021	15	224	20	226	4.3%	0.76 [0.40, 1.44]	
Horby 2021	215	1754	273	1800	63.9%	0.81 [0.68, 0.95]	
Rosas 2021	51	183	33	90	13.8%	0.76 [0.53, 1.09]	
Rutgers 2021	18	174	27	180	5.7%	0.69 [0.39, 1.21]	
Soin 2021	14	91	13	88	3.6%	1.04 [0.52, 2.09]	
Stone 2020	11	161	8	82	2.3%	0.70 [0.29, 1.67]	
Veiga 2021	7	65	11	64	2.3%	0.63 [0.26, 1.51]	
Total (95% CI)		2741		2624	100.0%	0.78 [0.68, 0.89]	•
Total events	342		408				
Heterogeneity: Chi ² =	: 3.57, df =	8 (P = 0).89); I ² = 0%				
Test for overall effect							0.01 0.1 1 10 100 Favours [experimental] Favours [control]

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



	Toci	lizuma	ab	0	Control			Mean Difference		Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	\$D	Total	Weight	IV, Random, 95% Cl		IV, Rando	m, 95% Cl		
Hamed 2021	23.27	8.96	26	21	19.85	27	25.7%	2.27 [-5.97, 10.51]		-	-		
Veiga 2021	11.3	8	65	14.7	8.2	64	74.3%	-3.40 [-6.20, -0.60]					
Total (95% CI)			91			91	100.0%	-1.94 [-6.80, 2.91]		•			
Heterogeneity: Tau² = Test for overall effect			•	= 1 (P =	0.20); l ^a	°= 39%	I		-100	-50 Favours Control) Favours To	50 50 cilizuma	100 b

Figure 7. Length of Hospital Stay

	То	cilizumab)		Control			Mean Difference		Mean Dif	ference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl		
Hamed 2021	3.92	7.99	26	9.96	16.73	27	24.1%	-6.04 [-13.06, 0.98]					
Rosas 2021	11.35	37.8981	294	17.1	50.9943	144	16.0%	-5.75 [-15.14, 3.64]			-		
Soin 2021	8.2	6.2	91	8.4	6.5	88	59.8%	-0.20 [-2.06, 1.66]		•	l i		
Total (95% CI)			411			259	100.0%	-2.50 [-6.80, 1.80]		•			
Heterogeneity: Tau ^z : Test for overall effect				(P = 0.1)	6); I² = 45%	ò			⊢ -100	-50 C Favours Control		l 50 cilizuma	100 ab

Adverse events

Figure 8. Length of ICU Stay

Study	Study duration days	Intervention 1	Intervention 2	r1/N1	r2/N2			AE		Ris C	sk of D	Bias E	Overall	Weights (%)	Risk ratio [95% Cl]
										Ŭ		-	Overall		
Mild to severe															
Salama C, 2020	60	Tocilizumab 8 mg/kg	Placebo	127/249	67/128	H	ł	_		_	_	_	_	10.61%	0.97 [0.79, 1.20]
Mild to severe		o myrky								-					
Stone JH, 2020	28	Tocilizumab 8mg/kg	Placebo	37/161	19/81	⊢	-	_		_	_	_	_	1.98%	0.98 [0.60, 1.59]
Moderate/severe		ongvig													
Hermine O, 2020	90	Tocilizumab 8mg/kg	Standard care	28/63	36/67	+•	ł	_		_	_	_		3.68%	0.83 [0.58, 1.18]
Moderate/severe		onging								-	-				
Wang D, 2021	14	Tocilizumab 400 mg	Standard care	20/34	4/31		⊢►	_	_	_	_	_	_	0.51%	4.56 [1.75, 11.87]
Mild to critical		400 Hig									-				
Rosas I, 2021	60	Tocilizumab 8mg/kg	Placebo	237/294	118/144	•				_	_	_	_	42.09%	0.98 [0.89, 1.08]
Moderate to critical		onging													
Soin AS, 2021	30	Tocilizumab 6 mg/kg/day	Standard care	33/91	22/88	ŀ	•	_	_	_	_	_	_	2.27%	1.45 [0.92, 2.28]
Moderate to critical		o mgrkgruay									-				
Veiga VC, 2021	29	Tocilizumab 8 mg/kg	Standard care	29/65	21/64	H	•	_		_	_	_	_	2.37%	1.36 [0.87, 2.12]
Severe		o myrky								-	-				
Salvarani C, 2020	30	Tocilizumab 8mg/kg	Standard care	13/60	5/63			_		_	_	_	_	0.50%	2.73 [1.04, 7.19]
Severe/critical		ongvig								•	-				
Rosas, IO, 2021	60	Tocilizumab 8 mg/kg once or twice	Placebo	320/430	147/210		I	• •						35.99%	1.06 [0.96, 1.18]
Heterogeneity: Q = 19.92	l, p = 0.01; l ² = 4.2%; τ^2 = 0.00														
								Risk of	bias	is as	sessed	i only for	randomized patients		
Risk of bias ratings:	Risk of Bias Do	nains:	Total:	1447											1.03 [0.97,,11#1]
Low Risk of Bias Some Concerns	A: Bias due to randomization B: Bias due to deviation from		Total events:	844	439										
High Risk of Bias	C: Bias due to deviation non D: Bias due to outcome mea	!			Intervention 1 bette	r	Interven	tion 2 better	r			Data s	ource: the COVID-	NMA initiative (ht	tps://covid-nma.com/)
	E: Bias due to selection of re														
						0.14 0.51	1.95 7.39								
						Risk I	Ratio								

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



Salama C, 2020 60 Mild to severe Stone JH, 2020 28 Moderate/severe Talaschian M, 2021 28	Intervention 1 Tocilizumab 8 mg/kg Tocilizumab 8 mg/kg	Intervention 2 Placebo Placebo	r1/N1 38/259	r2/N2 25/129	L.	A	B C	of Bias D I	E Overall	Risk Ratio [95% CI]
Mild to severe Stone JH, 2020 28 Moderate/severe	Tocilizumab 8mg/kg		38/259	25/129	H H H					
Mild to severe Stone JH, 2020 28 Moderate/severe Talaschian M, 2021 28	Tocilizumab 8mg/kg		38/259	25/129	H					
Moderate/severe Talaschian M, 2021 28	1711051	Placebo			1					13.56% 0.76 [0.48, 1.20]
			28/161	12/82	H-		2.2			7.37% 1.19 [0.64, 2.21]
	Tocilizumab 8 mg/kg once-off	Standard care	3/20	0/20		• 🕺	30			0.34% 7.00 [0.38, 127.32]
Hermine O, 2020 90 Moderate/severe	Tocilizumab 8mg/kg	Standard care	20/64	29/67	H		22			13.75% 0.72 [0.46, 1.14]
Wang D, 2021 14 Mild to critical	Tocilizumab 400 mg	Standard care	0/33	1/32		•	22			0.28% 0.32 [0.01, 7.66]
Rosas I, 2021 60 Moderate to critical	Tocilizumab 8mg/kg	Placebo	113/301	62/151	•		20			49.34% 0.91 [0.72, 1.16]
Soin AS, 2021 30 Moderate to critical	Tocilizumab 6 mg/kg/day	Standard care	18/90	15/90	H=-1		22			7.42% 1.20 [0.65, 2.23]
Veiga VC, 2021 29 Severe	Tocilizumab 8 mg/kg	Standard care	11/65	7/64		+ 🔛	20			3.66% 1.55 [0.64, 3.74]
Salvarani C, 2020 30 Severe/critical	Tocilizumab 8mg/kg	Standard care	1/60	2/66	• •	-	22			0.51% 0.55 [0.05, 5.91]
Gordon AC, 2021 90 Heterogeneity: Q = 6.95, p = 0.64; l ² = 0.0%; τ ² = 0	Tocilizumab 8 mg/kg	Standard care	9/366	11/412	H H		1			3.77% 0.92 [0.39, 2.20]

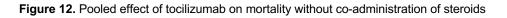
Figure 10. Pooled effect of tocilizumab on the incidence of serious adverse events. Source: covid-nma.com

	With Ste	roids	Standard of	f Care		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rando	om, 95% Cl	
Hamed 2021	2	26	5	27	1.5%	0.42 [0.09, 1.95]				
Hermine 2020	1	10	6	12	1.0%	0.20 [0.03, 1.40]	-		_	
Hermine 2021	18	224	24	226	9.5%	0.76 [0.42, 1.35]			_	
Horby 2021	457	1664	585	1721	63.7%	0.81 [0.73, 0.89]				
Rosas 2020	29	106	18	79	11.9%	1.20 [0.72, 2.00]		-	-	
Salama 2020	27	200	24	112	12.4%	0.63 [0.38, 1.04]				
Total (95% CI)		2230		2177	100.0%	0.80 [0.66, 0.97]		•		
Total events	534		662							
Heterogeneity: Tau ² =	= 0.01; Chi ^a	² = 6.01,	df = 5 (P = 0.	31); i^z = 1	17%					400
Test for overall effect	: Z = 2.32 (I	P = 0.02)				0.01 Fa	0.1 1 Ivours With Steroid	10 Favours control	100

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



	Without St	eroids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Hermine 2020	14	53	18	55	8.9%	0.81 [0.45, 1.45]	_ - • <u>+</u> _
Horby 2021	139	357	127	367	83.7%	1.13 [0.93, 1.36]	
Rosas 2020	29	188	10	65	7.0%	1.00 [0.52, 1.94]	_
Salama 2020	2	49	0	16	0.3%	1.70 [0.09, 33.67]	
Total (95% CI)		647		503	100.0%	1.09 [0.91, 1.29]	•
Total events	184		155				
Heterogeneity: Tau ² =	= 0.00; Chi ² =	1.26, df=	= 3 (P = 0	.74); I ^z	= 0%		
Test for overall effect							0.01 0.1 1 10 10 Favours Without Steroids Favours Control



	Tocilizu	mab	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
10.1.1 Requiring Oxy	gen Suppl	lementa	ation				
Hamed 2021	2	26	5	27	0.3%	0.42 [0.09, 1.95]	
Hermine 2020	7	64	8	67	0.8%	0.92 [0.35, 2.38]	
Hermine 2021	18	224	24	226	2.1%	0.76 [0.42, 1.35]	—
Horby 2021	175	935	202	933	21.5%	0.86 [0.72, 1.04]	-
Rosas 2021	6	78	2	44	0.3%	1.69 [0.36, 8.03]	
Salama 2020	26	259	11	129	1.6%	1.18 [0.60, 2.31]	
Salvarani 2020	2	60	1	66	0.1%	2.20 [0.20, 23.65]	
Stone 2020	9	161	3	82	0.4%	1.53 [0.43, 5.49]	
Subtotal (95% CI)		1807		1574	27.0%	0.88 [0.75, 1.04]	•
Total events	245		256				
Heterogeneity: Tau² =	0.00; Chř	z = 3.89	, df = 7 (F	P = 0.79	i); i² = 0%		
Test for overall effect:	Z = 1.50 (P = 0.13	3)				
10.1.2 Requiring Non	Invasive I	Mechan	ical Ven	tilation			
Horby 2021	296	819	350	867	47.4%	0.90 [0.79, 1.01]	
Rosas 2020	13	94	8	39	1.1%	0.67 [0.30, 1.50]	
Subtotal (95% CI)		913		906	48.5%	0.89 [0.79, 1.00]	•
Total events	309		358				
Heterogeneity: Tau ² =	0.00; Chř	² = 0.48	df = 1 (F	^o = 0.49); I ^z = 0%		
Test for overall effect:	Z = 1.91 (P = 0.08	i)				
10.1.3 Requiring Inva	sive Mech	hanical	Ventilati	on			
Horby 2021	125	268	142	294	23.1%	0.97 [0.81, 1.15]	+
Rosas 2020	20	113	9	55	1.4%	1.08 [0.53, 2.22]	
Subtotal (95% CI)		381	-	349	24.5%	0.97 [0.82, 1.15]	•
Total events	145		151				
Heterogeneity: Tau ² =	0.00; Chi	² = 0.09	. df = 1 (F	, = 0.76	i); I ² = 0%		
Test for overall effect:					//		
Total (95% CI)		3101		2829	100.0%	0.91 [0.83, 0.99]	•
Total events	699	0101	765	LULU	1001070	and a formal analy	'
Heterogeneity: Tau ² =		z-620		(P – 0 0	2\· 2 – ∩0	ĸ	
Test for overall effect:				(i = 0.8	2),1 = 05	v	'0.01 0.1 i 1'0 100'
Test for subgroup diff			•	2 (P – 0	186) IZ-1	n %.	Tocilizumab Control
reactor aduqtoup ulli	erences. (- U	.04, ul	2 (F - 0	.007,1 =1	0.0	

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	•Allocation: N/A	Intervention:	-Up to 17 years old	•Serum concentration of TCZ
A Study Evaluating Tocilizumab in Pediatric Patients with Covid 19 Recruiting	 Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: 	Tocilizumab Control: Standard of Care	-With COVID-19 disease	 •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
<u>Study Start:</u> January 15, 2022 <u>Completion date:</u> January 2, 2023	Treatment			 Clearance (CL) of TCZ Volume of distribution of TCZ Duration of 90% saturation of slL-6R Concentration of IL-6 Concentration of SlL-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			JUD	RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS				
Problem	No	Yes (11)		Var	ies	Uncertain		
Benefits	Large (1)	Moderate (10)	Small (1)	Trivial	Varies (1)	Lincortain		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	Mode	rate	Low (1)		Very low (10)		 Rated very low due to serious risk of bias, indrectness 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 Varies (5) (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. ٠