Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Among patients with COVID-19, should tocilizumab be used for treatment?

Updated by: Katherine Ruth O. Relato, MD, Carol Stephanie C. Tan-Lim, MD, MSc (Clinical Epidemiology), Natasha Ann R. Esteban-Ipac, MD

Initial review by: Ian Theodore Cabaluna, RPh, MD, GDip (Epi), Howell Henrian G Bayona, MSc, CSP-PASP

RECOMMENDATIONS

We recommend the addition of tocilizumab to systemic steroids in patients showing rapid respiratory deterioration and/or requiring high doses of oxygen (high-flow nasal cannula, noninvasive or invasive mechanical ventilation) and with elevated biomarkers of inflammation (CRP). *(Moderate certainty of evidence, Strong recommendation)*

We recommend against the use of tocilizumab among patients with COVID-19 infection who do not require oxygen. *(Very low certainty of evidence, Strong recommendation)*

Consensus issues
Report on adverse events, although an important outcome, was not rated as a critical outcome to be included in the decision making. The over-all assessment of the certainty of evidence is based only on critical outcomes identified by the consensus panel, hence, the quality of evidence was retained as moderate.

There is no new evidence on the use of tocilizumab among patients with COVID-19 infection who do not require oxygen. Given the lack of evidence, potential adverse effects and risks, this recommendation also considers indiscriminate use to avoid misuse or overuse of tocilizumab among patients who do not require oxygen.

PREVIOUS RECOMMENDATIONS

We recommend the addition of tocilizumab to systemic steroids in patients showing rapid respiratory deterioration and/or requiring high doses of oxygen (high-flow nasal cannula, noninvasive or invasive mechanical ventilation) and with elevated biomarkers of inflammation (CRP). *(Moderate certainty of evidence; Strong recommendation)*

We recommend against the use of tocilizumab among patients with COVID-19 infection who do not require oxygen. *(Very low certainty of evidence; Strong recommendation)*

Previous consensus issues
The high cost and limited availability of tocilizumab should be considered in our local setting. The indiscriminate use, potential adverse effects (i.e., leukemia, TB reactivation), risks, and lack of evidence of tocilizumab on COVID-19 patients who do not require oxygenation should be taken into consideration as well. Tocilizumab may also be administered in the earlier part of the therapy in order to prevent the occurrence of cytokine storm.

What's new in this version?

This version includes three (3) RCTs (Derde 2021, Hamed 2021, and Hermine 2021) as well as an update on previous trials (Hermine 2020).

Key Findings

Fifteen (15) randomized controlled clinical trials (RCTs) (N = 8,937) that investigated the effectiveness of tocilizumab among confirmed hospitalized COVID-19 patients compared to placebo and/or standard of care was found. Tocilizumab significantly reduced all-cause mortality, time to clinical improvement, and the need for mechanical ventilation, with no significant increase in adverse events among hospitalized patients.

Introduction

Tocilizumab is a humanized anti-IL-6Ra monoclonal antibody globally approved for management of various types of arthritis. IL-6 is an important cytokine in both acute and chronic inflammation. Tocilizumab binds to the IL-6 receptors, thus inhibiting inflammation by reducing circulating neutrophils, neutrophil infiltration, circulation of dendritic cells, and serum macrophage migration. Safety of tocilizumab intravenous and subcutaneous administration was reported with the most common adverse events being infections such as pneumonia and cellulitis. Elevated liver enzyme levels, neutropenia, and changes in lipid levels were reported. Serious adverse effects include myocardial infarction and stroke.[1]

Hyperinflammation contributes to the severity of COVID-19.[2] IL-6 is an important prognostic marker for survival of the disease. It is also independently associated with the severity and predictive outcome of ventilation and organ damage.[3] Recent WHO Therapeutic and COVID-19 Living Guideline strongly recommends the use of tocilizumab in severe or critical patients.

Review Methods

A systematic search was done from the date of last search May 18, 2021 until September 15, 2021 to check for new trials in the COVID-NMA living data. Trials found in the COVID-NMA were included. Search was done in Medline, Cochrane Library, Google scholar using free text, MeSH terms and advance search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2, and tocilizumab. Screening was done in various trial registries for ongoing trials. Preprint search was also done in medrxiv, chinaxiv and biorxiv. Randomized controlled trials on tocilizumab compared to placebo or standard of care on COVID-19 patients, regardless of severity were included.

Results

Characteristics of included studies

Fifteen (15) randomized controlled clinical trials (RCTs) (N = 8,937) that evaluated the effectiveness of tocilizumab among confirmed hospitalized COVID-19 patients compared to placebo or standard of care were found. All of the trials reviewed were also included in the COVID-NMA Living Data which was last updated on September 15, 2021. Three (3) of the 15 trials were preprints. The summary on the characteristics of included studies can be found in Appendix 2.

Four (4) studies were multinational trials [5-8], while the rest were conducted in the United Kingdom [9], France [10,11], Italy [12], USA [13], China [14], Brazil [15], India [16], the Netherlands [17], Iran [18], and Dubai.[19] Study participants in all trials were suspected/confirmed COVID-19 patients, 18 years old and above, and with either presence of pulmonary infiltrates or requiring supplemental oxygen. Six (6) trials [7,10-13,18] excluded

patients on mechanical ventilation at the start of the trial, while two (2) trials [10,11] enrolled critical patients admitted in the intensive care unit that were receiving respiratory or cardiovascular organ support. Four (4) trials included elevated laboratory markers such as C-reactive protein (CRP), d-dimer, and ferritin in their inclusion criteria.[12-14,18] Standard of care varied per study but usually involved the administration of anticoagulants, steroids, or anti-viral drugs (e.g., darunavir/cobicistat, darunavir/ritonavir, lopinavir/ritonavir, or remdesivir).[5,8,12] Two (2) of the trials included steroids with tocilizumab as intervention.[11,19] All studies evaluated tocilizumab given via the intravenous route. There were no studies that evaluated tocilizumab given subcutaneously. There were only few moderate cases (not requiring oxygen) (121/ 8,937, 1.35%) that were included in these trials.

Overall Certainty of Evidence

Eleven (11) out of 15 trials were open label trials and there was an imbalance in the administration of steroids and anti-viral drugs as part of the standard of care among the participants of the studies. There were serious risk of bias, inconsistency, and imprecision in one important outcome (adverse events), however, given that the adverse events were not rated as critical outcomes to be included in the decision making by the panel, the overall quality of evidence is retained to be moderate. The risk of bias summary is shown in Appendix 4. The GRADE evidence summary is presented in Appendix 5.

Effectiveness Outcomes

The COVID-NMA project provided pooled analysis for clinical improvement, time to clinical improvement, time to death, adverse events, and serious adverse events (last updated July, 7, 2021).[20] Results on mortality and the initiation of mechanical ventilation were also pooled showing significant benefit in reducing these outcomes.

Mortality

Based on 14 RCTs (N = 8,489), tocilizumab reduced all-cause mortality at day 14 to day 90 follow-up compared to standard of care (RR 0.88, 95% CI 0.82-0.94, I^2=0%). Tocilizumab significantly reduced all-cause mortality at day 28 (RR 0.88, 95% CI 0.82-0.95, I^2=7%) but had no significant effect on all-cause mortality at day 90 (RR 0.88, 95% CI 0.76-1.02, I^2=0%). Pooled effect of tocilizumab based on co-administration of steroids also significantly reduced mortality however, it was noted to have borderline heterogeneity with RR 0.86, 95% CI 0.79-0.93, I^2= 43%, P=0.07.

Subgroup analyses on the effect of tocilizumab on mortality stratified according to oxygen requirement and co-administration of steroids were done (Appendix 5). Subgroup according to oxygen requirement did not show significant benefit across groups, including those requiring oxygen supplementation (RR 0.89, 95% CI 0.76-1.04, I^2=0%); those requiring non-invasive ventilation (RR 0.89, 95% CI 0.79-1.00, I^2=0%); and those requiring invasive mechanical ventilation (RR 0.98, 95% CI 0.82-1.16, I^2=0%). A subgroup analysis by co-administration of steroids demonstrated significant reduction in mortality among patients who were also given steroids (RR 0.80, 95% CI 0.73-0.88, I^2=17%) however, there was no significant benefit among patients who were not given steroids (RR 1.08, 95% CI 0.91-1.29, I^2=0%).

Clinical improvement

Eight (8) RCTs (N = 5,585) showed no significant difference in clinical improvement at day 28 among patients given tocilizumab compared to standard of care with borderline heterogeneity (RR 1.06, 95% CI 0.99-1.12, I^2=39.6%, p=0.07). There was a significantly shorter time to clinical improvement among those given tocilizumab (HR 1.25, 95% CI 1.14-1.38, I^2=9.9%).

Need for mechanical ventilation

There was significant reduction in the need for mechanical ventilation among patients given tocilizumab compared to standard of care (RR 0.78, 95% CI 0.68-0.89, I^2=0%; 9 RCTs).

Safety Outcomes

There was no significant difference in the risk for adverse events (RR 1.23, 95% CI 0.93-1.62, I^2=81.3%) and serious adverse events between the tocilizumab group and the control group (RR 0.92, 95% CI 0.77-1.08, I^2=0%), however, there is significant heterogeneity with the risk for adverse events. Common adverse events noted with tocilizumab were abnormal liver function tests, leukopenia, and neutropenia.[12-15] There was no evidence for increased risk for serious secondary infection.[5-7,10,13]

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Infectious Diseases Society of America (IDSA) (as of September 14, 2021)	Suggests the use of tocilizumab in adult hospitalized patients with progressive severe or critical COVID-19 who have elevated markers in addition to standard of care (i.e., steroids). Severe COVID-19 cases are patients with SpO2 ≤ 94% on room air, while critical cases are those on mechanical ventilation and ECMO *(Low certainty of evidence, Conditional recommendation*).[21]
US National Institutes of Health (NIH) (as of September 15, 2021)	Recommends the use of tocilizumab in combination with dexamethasone in hospitalized patients exhibiting rapid respiratory decompensation. These are COVID-19 patients that are: (1) admitted to an ICU unit within 24 hours and who require mechanical ventilation, non-invasive ventilator (NIV) or high-flow nasal cannula (HFNC) and (2) non-ICU patients but requiring NIV or HFNC AND have significantly increased markers of inflammation *(Moderate certainty of evidence, other randomized trials or subgroup analyses of randomized trials).[22]*
World Health Organization (WHO) (as of September 24, 2021)	Recommends treatment with the use of IL-6 receptor blocker (tocilizumab or sarilumab) in severe to critical COVID-19 patients, with recommendation to give both corticosteroids and IL-6 receptor blocker in the said patients. This is based on a high certainty of evidence for mortality and mechanical ventilation.[4]

Research Gaps

As of September 16, 2021, there are 18 ongoing clinical trials on tocilizumab for COVID-19 patients registered on *clinicaltrials.gov* and EU Clinical Trials Register. Four (4) of these trials have been completed and are awaiting results.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					
Benefits	Large (2)	Moderate (7)	Small	Uncertain			• Tocilizumab reduces all-cause mortality with significant reduction in mortality on subgroup analysis by co-administration of steroids • There was significant reduction in the need for mechanical ventilation
Harm	Large	Small (7)	Uncertain (2)				• Tocilizumab showed no significant difference in the risk for adverse events and serious adverse events between the 2 groups
Certainty of Evidence	High (1)	Moderate	Low (3)	Very low (5)			• The overall quality of evidence is very low due serious risk of bias, inconsistency and imprecision in one important outcome.
Balance of effects	Favors drug (9)	Does not favor drug	Uncertain				• Patients given tocilizumab had significant benefit in all-cause mortality and need for mechanical ventilation, with no significant increase in adverse events.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (4)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (9)	Moderate Cost	Negligible cost	Moderate savings	Large savings	• Cost of Php 28,830.84 for retail price of 400mg/20ml, 20ml vial; total drug regimen cost per patient per treatment course would be Php 57,661.68

							• Issues on drug shortage and high demand
Certainty of evidence of required resources	No included studies (1)	Very low (1)	Low	Moderate (4)	High (3)		• The cost is regulated by Presidential Executive Order 104
Cost effectiveness	No included studies (5)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (3)			
Equity	Uncertain (2)	Reduced (3)	Probably no impact	Increased (4)			
Acceptability	Uncertain (3)	No	Yes (6)				
Feasibility	Uncertain (2)	No	Yes (7)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Tocilizumab	9/7/2021 5:09PM	16	13
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Tocilizumab	9/7/2021 9:05PM	24	12
COVID-NMA Initiative	Tocilizumab	9/7/2021 4:46PM	17	15
Google Scholar	Tocilizumab AND COVID AND randomized trial	9/7/2021 920PM	13	10
ClinicalTrials.gov	COVID-19 COVID-19 Pneumonia, Investigational Trials, Tocilizumab	9/15/2021 9:30PM	21	14
Chinese Clinical Trial Registry	COVID Tocilizumab	9/15/2021 9:40PM	3	0
EU Clinical Trials Register	COVID Tocilizumab	9/15/2021 9:50PM	6	4
Republic of Korea - Clinical Research Information Service	COVID Tocilizumab	9/15/2021 9:52PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	COVID Tocilizumab	9/15/2021 9:53 M	0	0
CenterWatch	COVID Tocilizumab	9/15/2021 9:56PM	0	0
chinaxiv.org	COVID Tocilizumab	9/15/2021 10:01PM	1	0
Medrxiv.org	COVID Tocilizumab Filter: May 18-Sept 7	9/15/2021 10:23PM	5	5
Biorxiv.org	COVID Tocilizumab Filter: May 18-Sept 7	9/15/2021 1025	0	0

Appendix 3: Characteristics of Included Studies

Title/Author	Study Design	Country	Population	Intervention Group(s)	Control	Outcomes
Horby 2021 RECOVERY	Open label RCT	United Kingdom	Suspected or confirmed COVID-19 patients N = 4,116	Tocilizumab 8 mg/kg	Standard 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	Adaptive RCT	United Kingdom, France, the Netherlands, Australia	ICU admitted critical COVID-19 patients AND receiving respiratory or cardiovascular organ support N = 755	Group 1: Tocilizumab 8 mg/kg Group 2: Sarilumab	Standard 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	Open label RCT	France	Moderate, severe or critical COVID-19 patients with oxygen levels of 3 L/min or higher but without non-invasive ventilation (NIV) or mechanical ventilation (MV) N = 131	Tocilizumab 8 mg/kg	Usual 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 RCT	Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA	Severe COVID-19 patients N = 452	Tocilizumab 8 mg/kg	Placebo	• Clinical status at day 28 • Mortality • Ventilator free days • Time to improvement • Time to hospital discharge • Adverse events
Salama 2020	Double-blind, placebo controlled RCT	USA, Mexico, Kenya, South Africa, Peru, Brazil	Hospitalized COVID-19 pneumonia patients not on continuous	Tocilizumab 8mg/kg	Placebo	• Invasive mechanical ventilation or ECMO • Mortality • Time to hospital discharge or readiness for discharge

			positive airway pressure, bilevel positive airway pressure, or mechanical ventilation. N = 388			• Time to at least a two-category improvement in clinical status • Time to clinical failure
Salvarani 2020	Open-label RCT	Italy	Non-ICU COVID-19 patients. N = 126	Tocilizumab 8 mg/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 mmHg
Stone 2020	Double-blind, placebo controlled RCT	USA	Confirmed COVID-19 patients not on oxygen above 10 L/minute N = 243	Tocilizumab 8 mg/kg	Placebo	• Mortality • Mechanical ventilation • Clinical worsening • Time to improvement • Time to death • Duration of supplemental O2 • Admission to ICU
Wang 2020	Open-label RCT	China	Moderate or severe COVID-19 patients with elevated IL-6. N = 65	Tocilizumab	Standard 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	Open-label RCT	Brazil	Severe or critical COVID-19 patients N = 129	Tocilizumab 8 mg/kg	Standard 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)	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 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

			N = 183			• Serious adverse events
Rutgers 2021 ***(Pre-print)***	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 N = 354	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	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 N = 40	Tocilizumab 8 mg/kg	Standard of care	• Clinical improvement • 28-day mortality • Time to improvement
New Studies Added (as of Sept 15, 2021)						
Derde 2021 ***(Pre-print)***	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 N = 2,274	Group 1: Tocilizumab 8 mg/kg Group 2: Sarilumab Group 3: Anakinra Group 4: Interferon B1a	Standard care	• Respiratory and cardiovascular organ support-free days • Survival • In-hospital mortality 90 days • Time to ICU discharge • Time to hospital discharge
Hamed 2021	Open label RCT	Dubai	Hospitalized COVID-19 patients AND lung infiltrates >50% of lung	Group 1: Methylprednisolone	Historical control group	• All-cause mortality day 45 • Admission to ICU • Length of ICU stay

			fields within 48 hrs admission, O2 saturation <93% at rest on room air N = 76	Group 2: Methylprednisolone and Tocilizumab		• Invasive ventilation • Days on ventilation • Length of hospital stay
Hermine 2021 (CORIMUNO-TOCI-DEX) ***(Pre-print)***	Open label RCT	France	Moderate to severe COVID-19 patients requiring oxygen but without ventilation support, high flow or mech vent, WHO class 5 N = 453	Tocilizumab 8 mg/kg at Day 1 PLUS Dexamethasone 10 mg/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

Appendix 4. Study Appraisal

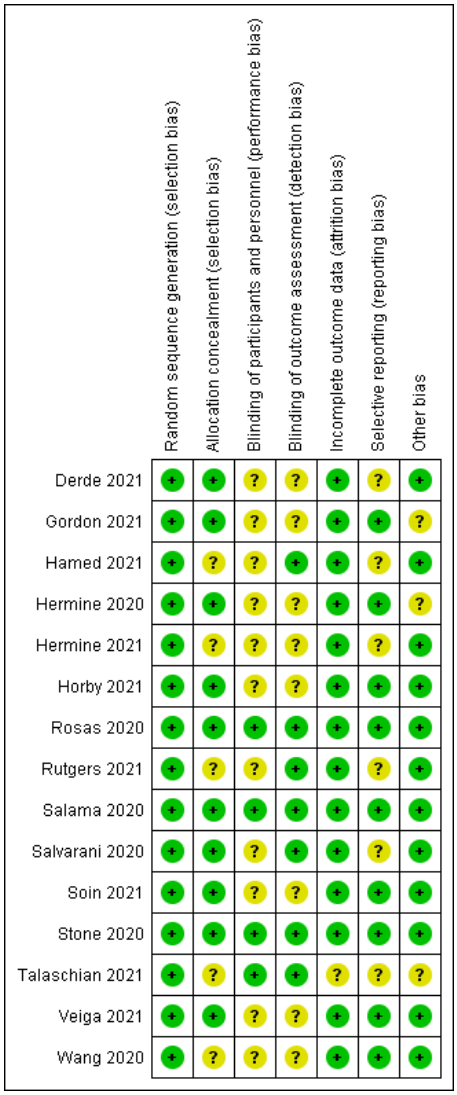

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): K. Relato; I. Cabaluna; A. Garcia
Question: Tocilizumab compared to standard of care in Covid-19
Bibliography: https://covid-nma.com/

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)												
14	randomised trials	serious [a]	not serious	not serious	not serious	none	1214/4475 (27.1%)	1165/4014 (29.0%)	**RR 0.88** (0.82 to 0.94)	**35 fewer per 1,000** (from 52 fewer to 17 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Clinical Improvement at Day 28												
8	randomised trials	serious [a]	not serious	not serious	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 0 fewer to 70 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Time to Clinical Improvement												
7	randomised trials	serious [a]	not serious	not serious	not serious	none	2183 participants	1325 participants	-	**HR 1.25 higher** (1.14 higher to 1.38 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for mechanical ventilation												
9	randomised trials	serious [a]	not serious	not serious	not serious	none	342/2741 (12.5%)	408/2624 (15.8%)	**RR 0.78** (0.68 to 0.89)	**34 fewer per 1,000** (from 50 fewer to 17 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse Events												
8	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	524/1033 (50.7%)	292/681 (42.9%)	**RR 1.23** (0.93 to 1.62)	**99 more per 1,000** (from 30 fewer to 266 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Serious Adverse Events												
10	randomised trials	serious [a]	not serious	not serious	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)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

a. some concerns due to imbalance in the administration of steroids and antivirals
b. Heterogeneity: I2=81.3%
c. Wide confidence interval with possibility for benefit and harm.

Appendix 6. Forest Plots

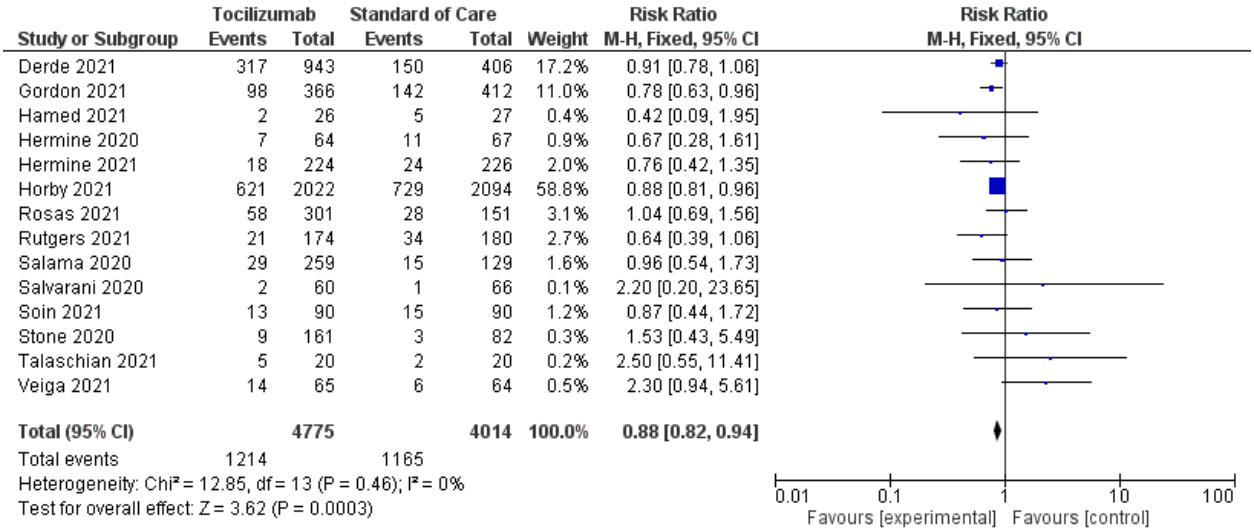

Figure 1. Pooled effect of tocilizumab on all-cause mortality (day 14 to day 90)

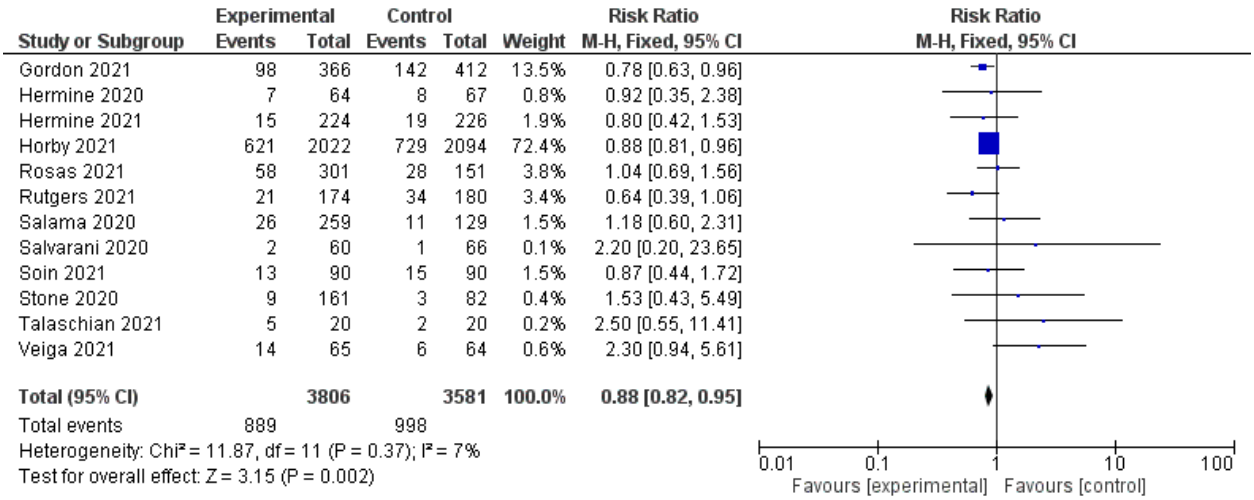

Figure 2. Pooled effect of tocilizumab on all-cause mortality day 28

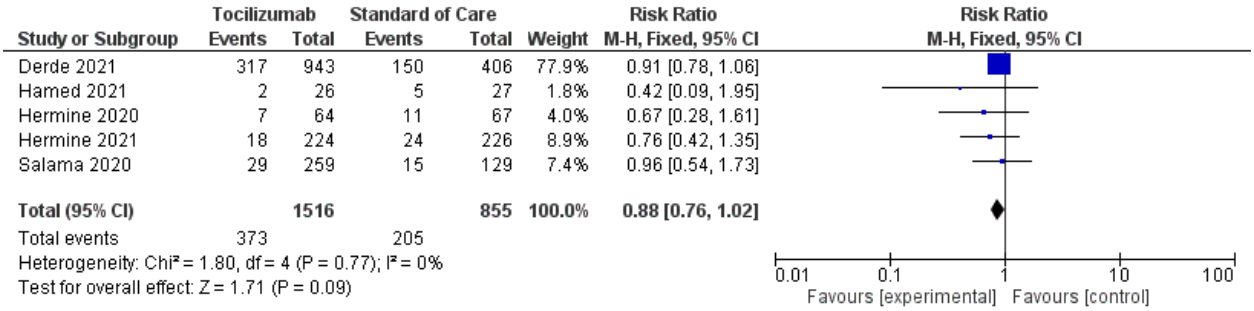

Figure 3. Pooled effect of tocilizumab on all-cause mortality day 90

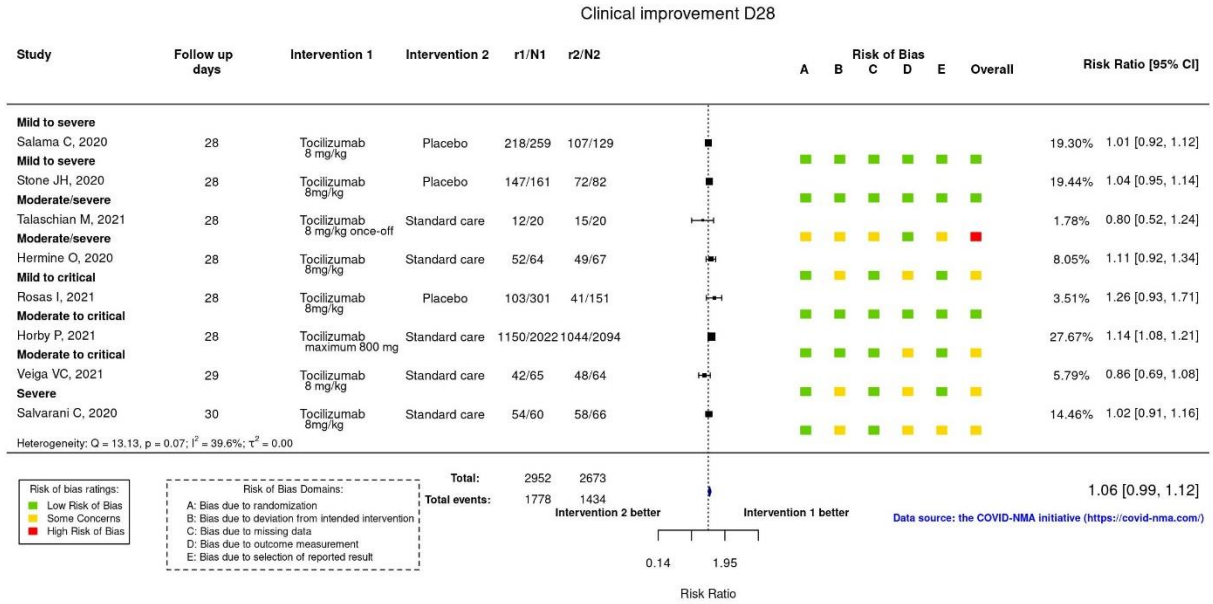

Figure 4. Pooled effect of tocilizumab on clinical improvement at day 28
(Source: covid-nma.com)

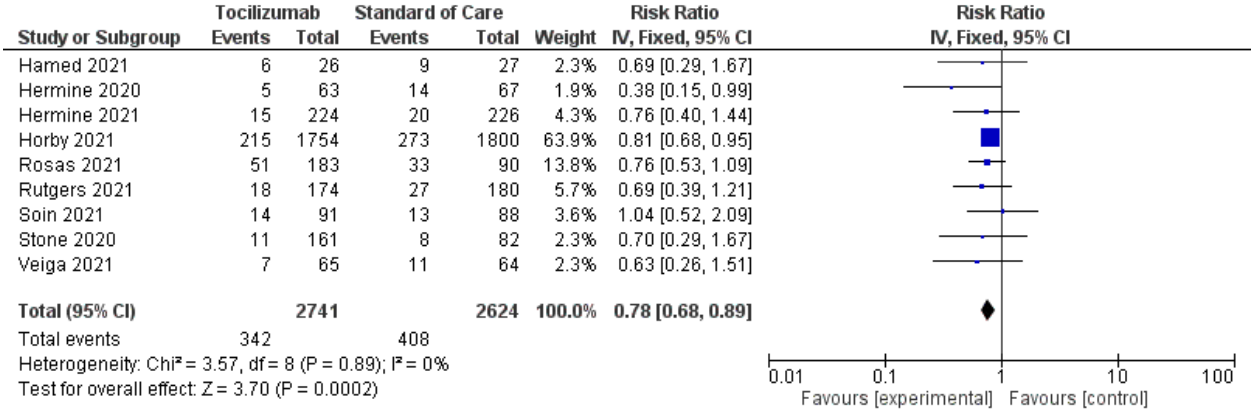

Figure 5. Pooled effect of tocilizumab on initiation of mechanical ventilation

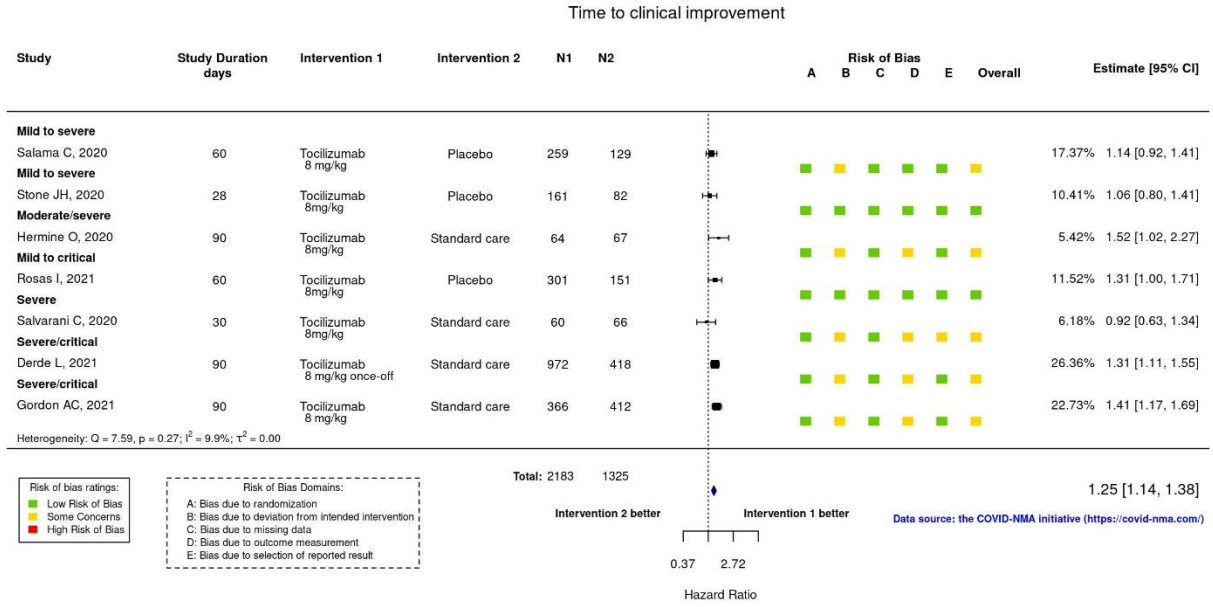

Figure 6. Pooled effect of tocilizumab on time to clinical improvement (hazard ratio)
(Source: covid-nma.com)

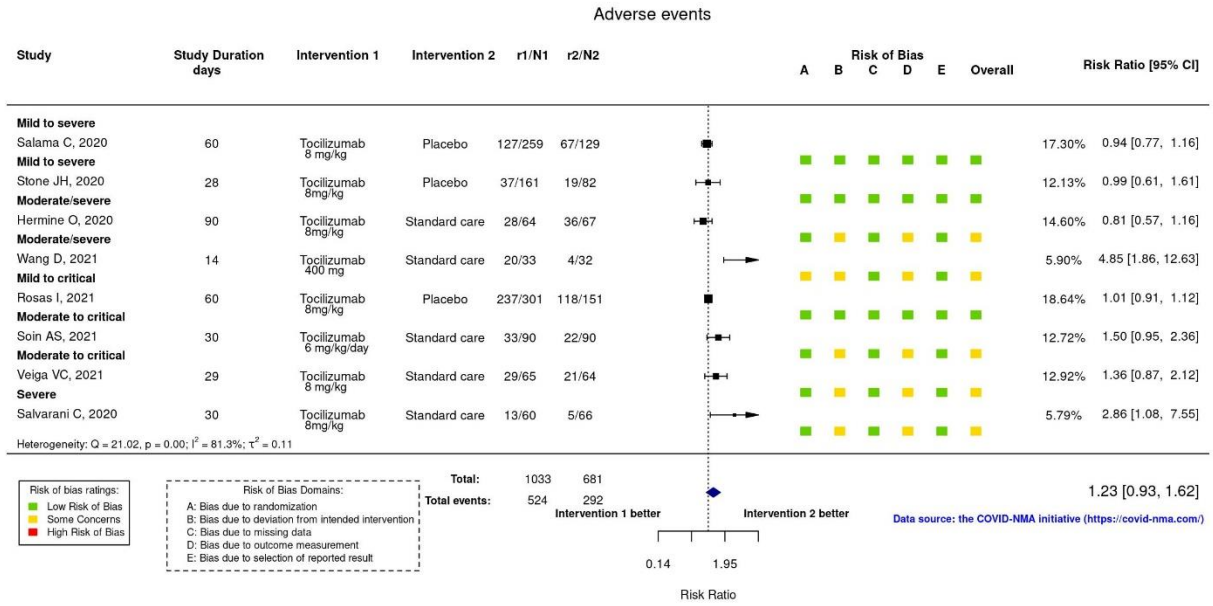

Figure 7. Pooled effect of tocilizumab on the incidence of adverse events
(Source: covid-nma.com)

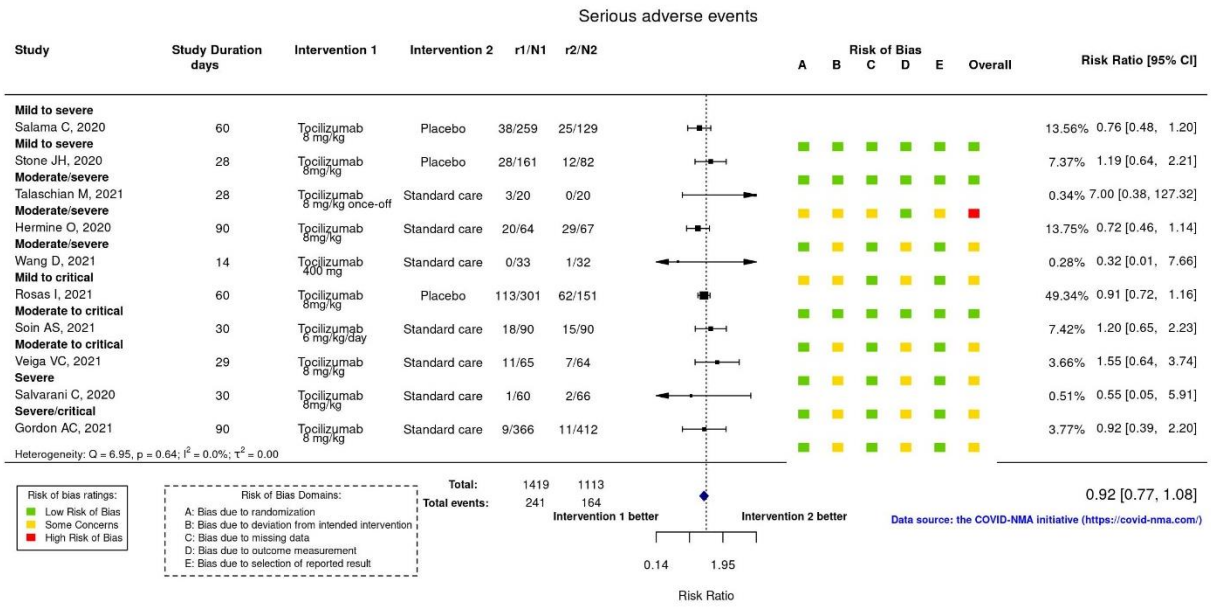

Figure 8. Pooled effect of tocilizumab on the incidence of serious adverse events
(Source: covid-nma.com)

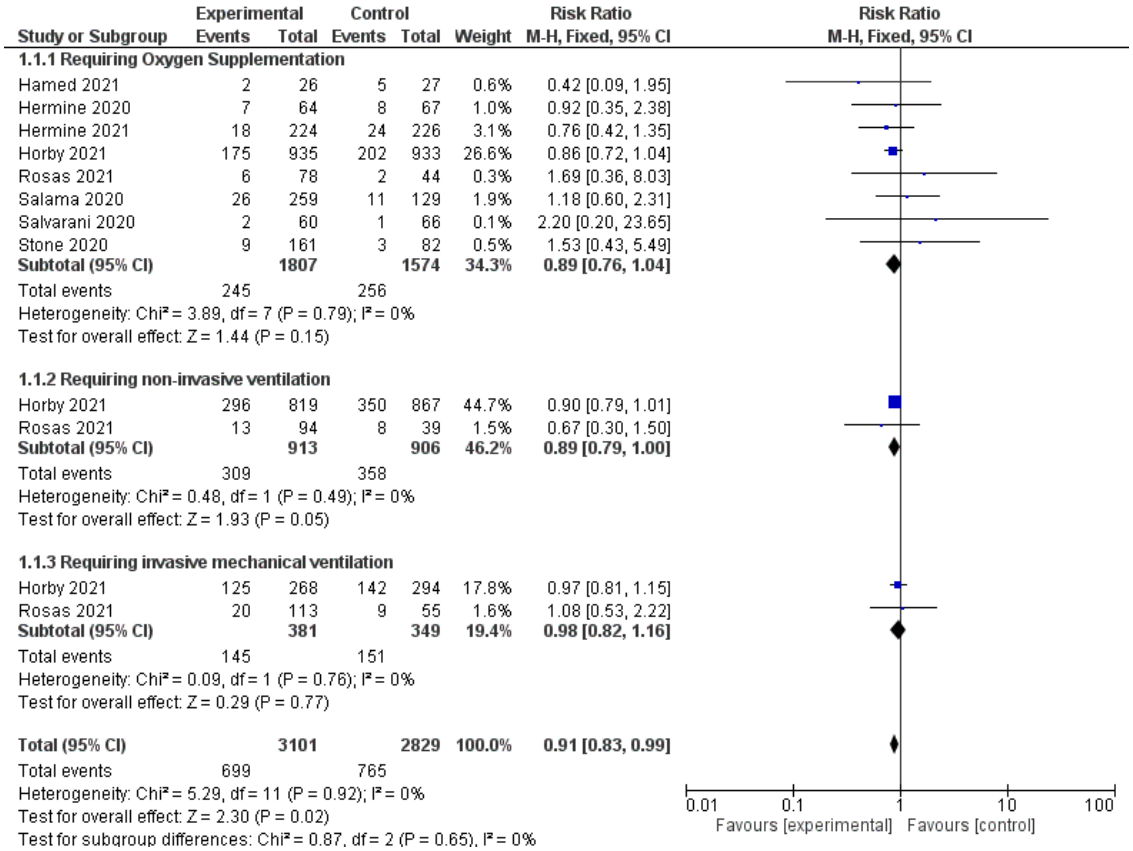

Figure 9. Pooled effect of tocilizumab on mortality according to oxygen requirement

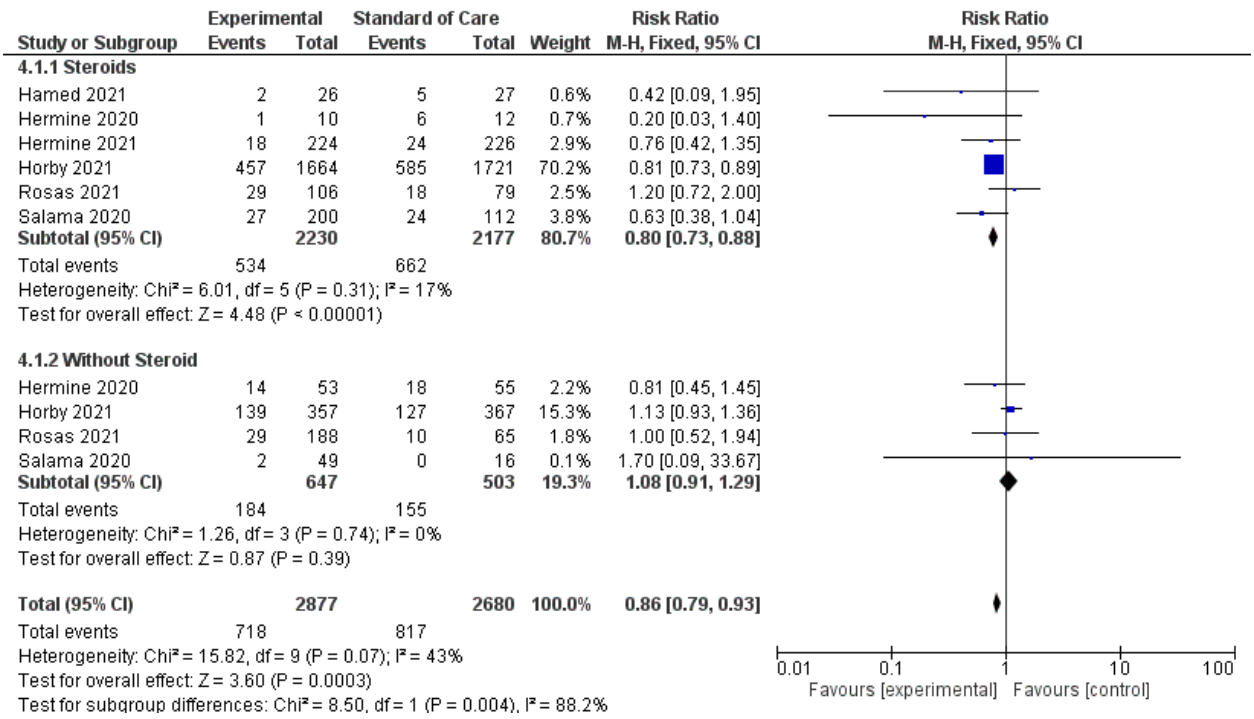

Figure 10. Pooled effect of tocilizumab on mortality with and without co-administration of steroids

Appendix 7. Pooled Results of Trials

Outcomes	Pooled Relative Risk	95% CI	Certainty of evidence (GRADE)
All-cause mortality (14 RCTs, N = 8,489)	0.88	0.82 to 0.94	Moderate
Clinical improvement D28 (8 RCTs, N = 5,625)	1.06	0.99 to 1.12	Moderate
Need for mechanical ventilation (9 RCTs, N = 5,365)	0.78	0.68 to 0.89	Moderate
Time to clinical improvement (Hazard ratio) (7 RCTs, N = 3,508)	1.25	1.14 to 1.38	Moderate
Adverse events (8 RCTs, N = 1,714)	1.23	0.93 to 1.62	Very Low
Serious adverse events (10 RCTs, N = 2,532)	0.92	0.77 to 1.08	Moderate

Appendix 8. Subgroup Analysis

	Pooled Relative Risk	95% CI	Certainty of Evidence
By oxygen requirement			
Requiring O2 supplementation (8 RCTs, N = 3,381)	0.89	0.76 to 1.04	Low
Requiring non-invasive ventilation (2 RCTs, N = 1,819)	0.89	0.79 to 1.00	Low
Requiring mechanical ventilation (2 RCTs, N = 730)	0.98	0.82 to 1.16	Low
By co-administration with steroids			
With steroids (6 RCTs, N = 4,407)	0.80	0.73 to 0.88	Moderate
Without steroids (4 RCTs, N = 1,150)	1.08	0.91 to 1.29	Low

Appendix 9. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Tocilizumab in COVID-19 Pneumonia (TOCIVID-19)	No age limit, COVID-19 confirmed by RT-PCR, hospitalized due to clinical/instrumental diagnosis of pneumonia, oxygen saturation ≤93% or requiring oxygen therapy or mechanical ventilation either non-invasive or invasive (intubated) (N = 402)	Experimental: Tocilizumab 8 mg/kg (up to a maximum of 800mg per dose). A second administration (same dose) can be given after 12 hours if respiratory function has not recovered, at discretion of the Investigator.	Primary: Lethality rate two weeks after registration	Single-arm, open-label, parallel cohort
2. Efficacy of Early Administration of Tocilizumab in COVID-19 Patients *Terminated*	>18 years old, RT-PCR confirmed COVID-19 patients, hospitalized due to clinical or instrumental diagnosis, presence of ARDS, with at least one of the ff: temperature of > 38C in the past two days, CRP >/= 10mg/dl, CRP increase of at least 2x the basal value (N = 126)	Experimental: Tocilizumab within 8 hours from entering the study plus standard of care; 8 mg/kg IV up to a maximum of 800mg with repetition of the same dosage after 12 hours Control: Standard of care	Primary: Entry into intensive care with invasive mechanical ventilation or death from any cause or clinical aggravation	Randomized parallel, open label
3. A Study to Investigate Intravenous Tocilizumab in Participants with Moderate to Severe COVID-19 Pneumonia (MARIPOSA) **Completed**	>18 years old, confirmed COVID-19 by RT-PCR Severe patients: SpO2 </= 93% or PaO2/FiO2 < 300 mmHg Moderate patients: CRP > 2 x upper limit of normal (ULN) is required	Experimental: Tocilizumab 4 mg/kg IV plus standard of care Active Comparator: Tocilizumab 8 mg/kg plus standard of care	Primary:Area Under the Curve from Day 0-28 (AUC0-d28) of Tocilizumab, Secondary: • Maximum Serum Concentration (Cmax) of Tocilizumab • Clearance (CL) of Tocilizumab • Volume of the Central Compartment (Vc) of Tocilizumab • Serum Concentration of C-reactive Protein (CRP) • Serum Concentration of Ferritin • Serum Concentration of Soluble Interleukin-6 Receptor • Serum Concentration of Interleukin-6 (IL-6)	Randomized, parallel, open label
4. A Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia (EMPACTA)	>18 years old, hospitalized COVID-19 pneumonia confirmed by RT-PCR and radiographic imaging, spO2 <94% while on ambient air (N = 388)	Experimental: Tocilizumab 8 mg/kg maximum dose 800mg plus standard of care Control: Placebo plus standard of care	Primary: Cumulative proportion of participants requiring mechanical ventilation by day 28	Randomized Parallel, Double-blind, Placebo-controlled
5. A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared with Remdesivir Plus Placebo in Hospitalized Participants with Severe COVID-19 Pneumonia (REMDACTA)	>/= 12 years old, hospitalized with COVID-19 pneumonia confirmed by RT-PCR and evidenced by chest X-ray or CT scan Requiring > 6 L/min supplemental oxygen to maintain SpO2 > 93%	Experimental: Remdesivir plus Tocillizumab Control: Remdesivir plus Placebo	Primary: Time from randomization to hospital discharge or ready for discharge day 28	Randomized, parallel, doiuble-blind

Completed	(N = 649)			
6. The Use of Tocilizumab in the Management of Patients Who Have Severe COVID-19 With Suspected Pulmonary Hyperinflammation	>/= 18 years old, RT-PCR positive, acute respiratory failure radiologic pneumonia, breathing spontaneously >50% Oxygen and MEWS score >7, if intubated PaO2/Fio2 </= 200 and PEEP >5 cm H2O (N = 500)	Experimental: Tocilizumab 8 mg/kg max 800mg Control: Placebo	Survival	Randomized, parallel, open label
7. Randomized, Unicentric, Open, Controlled Clinical Trial, in Phase III to Demonstrate the Effectiveness of Tocilizumab	18 -to 99 years old, bilateral pneumonia by SARS-COV-2 without response in 48 to 72 hours after starting the treatment according to local protocol, persistent elevated inflammatory markers (N = 60)	Experimental: Tocilizumab >75 kg = 600mg, <75kg = 400mg Control: Methylprednisolone 250mg IV for 3 days	Primary: Respiratory situation at 24 hours Secondary: Immune hyperactivation situation Mechanical ventilation In-hospital mortality	Randomized, parallel, open
8. Checkpoint Blockade in COVID-19 Pandemic (COPERNICO)	18 to 80 years old, confirmed COVID-19 with RT-PCR, or IgM, IgG, diagnostic confirmation of pneumonia on x-ray and CT scan, ARDS, SOFA score </= 3, total lymphocyte <0.8x106/mL, SpO2 </=92%, life expectancy of >10 years	Experimental: Tocilizumab 8 mg/kg plus Pembrolizumab 200mg Control: Standard of care	Primary: Percentage of patients with normalization of SpO2 ≥ 96% on room air	Randomized parallel, open-label
9. Low-dose Tocilizumab Versus Standard of Care in Hospitalized Patients With COVID-19 (COVIDOSE-2)	≥18 years old hospitalized, T ≥ 38 degrees C, positive test for active SARS-CoV-2 infection, radiographic evidence of infiltrates on chest radiograph (CXR) or computed tomography (CT) (N = 332)	Experimental sub study A: Tocilizumab 40mg Experimental sub study A: Tocilizumab 120mg Control A: Tocilizumab free standard of care Experimental sub study B: Tocilizumab 40mg Experimental sub study B: Tocilizumab 120mg Control B: Tocilizumab 400mg or 8mg/kg plus standard of care	Primary: Time to recovery	Randomized parallel, open label
10. COVID 19: Experimental use of tocilizumab (Roactemra®) in severe SARS-CoV-2 related pneumonia.	Positive COVID status as defined by positive RT-PCR, hospitalized patients aged ≥ 18 and ≤ 75 years old Signs of severe COVID-19 pneumonia (3 of the following): patient wheezing or unable to speak in full sentences while at rest/with minimal effort, respiratory rate >22, PaO2 <65 mmHg or SpO2 <90%, repeated chest imaging is significantly worsening despite being on standard of care, which may	Experimental: Tocilizumab Control: Standard of care	Clinical status assessed using a 7-category ordinal scale at Day 28	Randomized open label

	include anti-viral treatment, low dose steroids and antibiotics.			
11. A randomized clinical trial (IIIb) of eficacy of a single dose of Tocilizumab or a combination of Tocilizumab plus Vitamin D (single IM dose) for the treatment of the COVID-19 hyperimmune complication. Assessment of IL-6.	Moderate to severe COVID-19 patients (WHO severity scale 4-7) needing oxygen therapy At least 2 of the following: Dímer D> 1.500, CRP> 60 or Ferritin >800 Alternatively, IL-6 >40	Experimental: Tocilizumab plus Vitamin D3 2000 IU Control: Tocilizumab	Global survival rate	Randomized, open label
12. A prospective, randomized, double blinded placebo-controlled trial to evaluate the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia (TOC-COVID)	≥ 18 years old, proof of SARS-CoV-2, severe respiratory failure: ambient air SpO2 ≤ 92% or need of ≥ 6L O2/min or NIV (non-invasive ventilation) or IMV (invasive mechanical ventilation)	Experimental: Tocilizumab Control: Placebo	Ventilator free days (d) (VFD) in the first 28 days after randomization	Randomized double-blind placebo-controlled
13. A multi-center, randomized, open-label study in patients with COVID-19 and respiratory distress not requiring mechanical ventilation, to compare standard-of-care with anakinra and tocilizumab treatment. The Immunomodulation-CoV Assessment (ImmCoVA) study	Age ≥18 years old, confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay < 3 days prior to screening SARS-CoV-2 infection with duration at least 7 days (as determined by onset of symptoms), 5 liters/minute of oxygen for at least 8 hours to maintain SpO2 at ≥93%, CRP > 70 mg/L with no non-SARS-Cov2 infections, Ferritin > 500 µg/L, at least two points on a scale of 0-3 where 1 point is awarded for each value of: lymphocytes < 1x 10(9)/L; D-dimer ≥ 0.5 mg/L and; Lactate Dehydrogenase ≥ 8 microkatal/L	Experimental: Anakinra and Tocilizumab Control: standard of care	Time to recovery [Time Frame: Day 1 through Day 29]	Randomized, open label
14. Trial of Tocilizumab for Treatment of Severe COVID-19: ARCHITECTS	Hospitalized with COVID-19 pneumonia, based on chest X-ray or CT scan AND Evidence of hyperinflammation: IL-6>40pg/mL (if available) OR CRP >2 mg/dL OR ferritin >2000 ng/mL AND iv. One or more of the following: impending need for requiring invasive or non-invasive mechanical ventilation OR shock requiring vasopressor (without evidence of bacterial / fungal infection) OR need for extracorporeal membrane oxygenation (ECMO) OR severe, refractor ARDS (PaO2/FiO2<200 mmHg)	Experimental: Tocilizumab Control: Placebo	Clinical status (on a 7-point ordinal scale) at day 28	Randomized, double blind Placebo control
15. CORIMUNO-19 - Tocilizumab Trial - TOCI (CORIMUNO-TOCI) 2	Patients included in the CORIMUNO-19 cohort Patients belonging to one of the 2 following groups:	Experimental: Tocilizumab 8mg/kg day 1, if no response second injection Day 3 Control:	Survival without needs of ventilator utilization WHO progression scale <=5	Randomized, parallel open label

	Group 1: Cases meeting all of the following criteria: Requiring more than 3L/min of oxygen, OMS/WHO progression scale = 5, No NIV or High flow Group 2: Cases meeting all of the following criteria Respiratory failure AND (requiring mechanical ventilation OR NIV OR High flow), WHO progression scale >=6, No do-not-resuscitate order (DNR order)	Standard of care	Cumulative incidence of successful tracheal extubation WHO progression scale <=7	
16. Treatment of COVID-19 Patients with Anti-interleukin Drugs (COV-AID)	Recent (≥ 6 days of flu-like symptoms or malaise yet ≤16 days of flu-like symptoms or malaise prior to randomization) infection with COVID-19. Confident COVID-19 diagnosis Presence of hypoxia signs of cytokine release syndrome Chest X-ray or CT scan showing bilateral infiltrates within last 2 days Admitted to specialized COVID-19 ward or an ICU ward taking care of COVID-19 patients Age ≥ 18 years old	Experimental: Anakinra, Siltuximab, Tocilizumab Control: Placebo and standard of care	Time to Clinical Improvement	Randomized open label
17. COVID-19: Salvage Tocilizumab as a Rescue Measures (COVISTORM) **Completed**	Hospitalized with COVID-19 disease Age >/= 18 years old SARS-CoV-2 NhO positive SpO2 </93% on ambient air or respiratory rate >30 /min Any 2 of the 4: P-IL-6 > 2 x ULN / P-ferritin > 2 x ULN / P-FIDD >1.5 mg/l / P- CRP >40 mg/l without obvious presence of bacterial infection (normal values: P -IL-6 <5.9 ng/l; P-ferritin, men 30-400 mikrog/l, women 13-150 mikrog/l ; P-FIDD (Fibrin degradation products, D-dimer) <0.5 mg/l; P-CRP <10 mg/l)	Experimental: Tocilizumab Control: Standard of care	Clinical status at day 28	Randomized Parallel Open Label
18. Efficacy of Tocilizumab in Modifying the Inflammatory Parameters of Patients With COVID-19 (COVITOZ-01) (COVITOZ-01) *Terminated*	> 18 years of age, mild-moderate SARS-CoV-2 pneumonia confirmed microbiologically ≤7 days before randomization, and presents: a. Basal oxygen saturation> 90% b. CURB-65 ≤1 c. PaO2 / FiO2≥300 or SatO2 / FiO2≥315 The patient is hospitalized or meets hospital admission criteria; the patient is not expected to enter the ICU or die in the next 24 hours.	Experimental 1: Tocilizumab single dose and standard of care Experimental 2: Tocilizumab two doses and standard of care Control: Standard of care	Change in IL-12 values in the 3 study groups from the start of treatment (D0) and on days D + 1 and D + 3	Randomized single group open label