TOCILIZUMAB

RECOMMENDATION

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 markers of inflammation (CRP > 75 mg/L). *(Moderate quality of evidence; Strong recommendation)*

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

Consensus Issues

The high cost and limited availability of tocilizumab should be considered in our local setting. The potential indiscriminate use, potential adverse effects (i.e., leukemia, TB reactivation), and lack of evidence of tocilizumab on COVID-19 patients who do not require oxygenation were additional factors considered by the panel in strongly recommending against the use of tocilizumab in patients not requiring oxygen.

*Contraindications to tocilizumab
Immunocompromised or on immunosuppressive agents
Neutropenia with ANC < 500 cells/ml
Transaminitis with AST or ALT > 5x the upper limit of normal
Thrombocytopenia with platelet count < 50,000 cells/ml
Serious, uncontrolled bacterial super-infection, fungal infection
Active diverticulitis, bowel perforation, or at increased risk for bowel perforation
Active TB infection or active zoster

EVIDENCE SUMMARY

Should tocilizumab be used for the treatment of hospitalized patients with COVID-19?

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Key Findings

Nine randomized controlled clinical trials (RCTs) (n=6,405) that evaluated the effectiveness of tocilizumab among confirmed hospitalized COVID-19 patients compared to placebo and/or standard of care was found. Low to moderate quality evidence shows that tocilizumab has a beneficial effect in hospitalized COVID-19 patients on clinical improvement, mortality reduction, and initiation of mechanical ventilation.

Introduction

Tocilizumab is an immunosuppressive drug used for treating various forms of arthritis. As a monoclonal antibody that binds to interleukin-6 (IL-6), it inhibits IL-6 signaling which consequently reduces inflammation. Although a number of studies have demonstrated its safety [1-4], there is also evidence showing that its use may be associated with serious adverse events (e.g., infections, neutropenia, hypercholesterolemia, hepatotoxicity) [5].

Systemic hyperinflammation has been proposed as a key characteristic of the disease in patients with severe COVID-19 [6] Recent observational studies have also shown significantly higher IL-6 levels and other inflammatory cytokines among non-survivors.[7,8] Intravenous administration of tocilizumab is currently being used as one of the experimental treatments for patients with COVID-19.

Review Methods

Trials found in the COVID-NMA living data (as of February 12, 2021) were included. Screening after their last search was done in Medline, Cochrane Library, MedRivx to check for newer trials. Randomized controlled trials on tocilizumab compared to placebo or standard of care on COVID-19 patients, regardless of severity were included.

Results

Nine randomized controlled clinical trials (RCTs) (n=6,405) that evaluated the effectiveness of tocilizumab among confirmed hospitalized COVID-19 patients compared to placebo and/or standard of care was found.[9-17] All of the trials we reviewed were also included in the COVID-NMA Living Data which was last updated on February 12, 2021.[18] Four were pre-prints as of February 13, 2021.[12,14,15,17]

Appendix 1 summarizes characteristics of included studies. Three studies were multinational trials [13-15] while 6 were conducted in the USA [11], Brazil [16], China [12], Italy [9], France [10] and the United Kingdom [17]. Study participants in all 9 trials were suspected/confirmed COVID-19 patients, 18 years old and above, and with either presence of pulmonary infiltrates or requiring supplemental oxygen. Four trials [9-11,13] excluded patients on mechanical ventilation at the start of the trial, while 1 trial [14] enrolled critical patients admitted in the intensive care unit and were receiving respiratory or cardiovascular organ support. Three trials included elevated laboratory markers such as C-reactive protein (CRP) and d-dimer in their inclusion criteria. [9,11,12] Standard of care varied per study but usually involved the administration of anticoagulants, steroids, or anti-viral drugs (darunavir/cobicistat, darunavir/ritonavir, lopinavir/ritonavir, remdesivir

[9,19]). There were only few moderate cases (not requiring oxygen) (117/6405, 1.8%) that were included in these trials.

The COVID-NMA project provided pooled analysis for mortality, clinical improvement, time to clinical improvement, time to death, adverse events, and serious adverse events (last updated: February 12, 2021)[18]. We also pooled the results on the initiation of mechanical ventilation.

Tocilizumab showed significant benefit in reducing mortality, initiation of mechanical ventilation and clinical improvement. Based on 8 RCTs (N=6,363), tocilizumab was able to reduced all-cause mortality in severe COVID-19 patients (RR = 0.89, 95% CI: 0.82 to 0.97). See Table 2 and Figure 1.

Tocilizumab prevented the initiation of mechanical ventilation (RR 0.78, 95%CI 0.68 to 0.90) in 6 RCTs (N=4,452). From 7 RCTs (N=5,585), the proportion of patients that improved clinically was higher among those given tocilizumab, but this difference was not statistically significant (RR = 1.06; 95% CI: 1.00 to 1.13).

Tocilizumab did not increase the risk for adverse events (RR = 1.23, 95% CI: 0.87 to 1.72) and serious adverse events (RR = 0.89, 95% CI: 0.75 to1.06). Common adverse events noted with tocilizumab were abnormal liver function tests, leukopenia and neutropenia.[9,11,12,16] There was no evidence for increased risk for serious secondary infection.[10,11,13-15]

Subgroup analyses on the effect of tocilizumab on mortality stratified according to severity and co-administration of steroids were done (Appendix 4). Among severe COVID-19 cases, a non-significant trend toward benefit was found. Patients who were also given steroids demonstrated significantly higher mortality reduction (RR 0.81, 95%CI 0.73 to 0.89).

Recommendations from Other Groups

Both IDSA and US-NIH recommend the use of tocilizumab in hospitalized patients. [20,21]

As of February 17, 2021, Infectious Disease Society of America (IDSA) suggest 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). (Low quality evidence, Conditional Recommendation).

As of March 5, 2021, US-NIH recommends the use of tocilizumab in combination with dexamethasone in hospitalized patients exhibiting rapid respiratory decompensation (i.e. admitted to an ICU unit and who require mechanical ventilation, non-invasive mechanical ventilator (NIV) or high-flow nasal cannula (HFNC); non-ICU but who requires NIV or HFNC AND have significantly increased markers of inflammation. (BIIA Moderate recommendation)

Research Gaps

As of February 10, 2021, there are 35 ongoing clinical trials on tocilizumab for COVID-19 patients registered on ClinicalTrials.gov.

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Appendix 1: Characteristics of Included Studies

Title/Author	Study design	Country	Population	Intervention Group(s)	Control	Outcomes
Horby* 2021 RECOVERY N=4116	Randomized Open label trial	United Kingdom	Suspected or confirmed	Tocilizumab	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 N=755	Adaptive RCT	United Kingdom, France, the Netherlands, Australia	ICU admitted critical Covid-19 patients AND receiving respiratory or cardiovascular organ support	Group 1: Tocilizumab 8 mg/kg Group 2: Sarilumab	Standard care	Respiratory and cardiovascular organ support-free days Survival Time to ICU discharge Time to hospital discharge

						WHO scale at day 14 Progression to invasive mechanical ventilation, ECMO or death Serious adverse events
Hermine 2020 N= 131	Open label RCT	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	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 N=452	Double-blind, placebo controlled RCT	Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA	Severe Covid-19 patients	Tocilizumab	Placebo	Clinical status at day 28 Mortality Ventilator free days Time to improvement Time to hospital discharge Adverse events

Salama 2020 N=388	Double-blind, placebo controlled RCT	USA, Mexico, Kenya, South Africa, Peru, Brazil	Hospitalized Covid-19 pneumonia patients n**ot** on continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation.	Tocilizumab	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	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	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 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	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

**Preprints*

Appendix 2: GRADE Evidence Profile

Author(s): 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 28 days)												
8	randomised trials	serious [a]	not serious	not serious	not serious [b]	none	810/3298 (24.6%)	893/3065 (29.1%)	**RR 0.89** (0.82 to 0.97)	**32 fewer per 1,000** (from 52 fewer to 9 fewer)	⨁⨁⨁◯ MODERATE	
Clinical Improvement (follow up: range 14 days to 28 days)												
7	randomised trials	serious [a]	not serious	not serious	not serious	none	1709/2932 (58.3%)	1365/2653 (51.5%)	**RR 1.06** (1.00 to 1.13)	**31 more per 1,000** (from 0 fewer to 67 more)	⨁⨁⨁◯ MODERATE	
Initiation of mechanical ventilation (follow up: 28 days)												
6	randomised trials	serious [a]	not serious	not serious	not serious [b]	none	295/2286 (12.9%)	344/2166 (15.9%)	**RR 0.78** (0.68 to 0.90)	**35 fewer per 1,000** (from 51 fewer to 16 fewer)	⨁⨁⨁◯ MODERATE	
Adverse Events												
7	randomised trials	not serious	serious [c]	not serious	serious [b]	none	491/944 (52.0%)	270/586 (46.1%)	**RR 1.11** (0.89 to 1.39)	**51 more per 1,000** (from 51 fewer to 180 more)	⨁⨁◯◯ LOW	
Serious Adverse Events												

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)		
8	randomised trials	not serious	not serious	not serious	serious [b]	none	220/1297 (17.0%)	149/988 (15.1%)	**RR 0.89** (0.75 to 1.06)	**17 fewer per 1,000** (from 38 fewer to 9 more)	⨁⨁⨁◯ MODERATE	

Time to clinical improvement

5	randomised trials	serious [a]	not serious	not serious	not serious	none	841 participants	1151 participants	**Rate ratio 1.27** (1.13 to 1.43) [Clinical Improvement]	**-- per 1000 patient(s) per years** (from -- to --)	⨁⨁⨁◯ MODERATE	
							-	88.9%		**-- per 1000 patient(s) per years** (from -- to --)		

Time to death

3	randomised trials	serious [a]	not serious	not serious	not serious	none	561 participants	591 participants	**HR 0.65** (0.51 to 0.83) [Time to death]	**13 fewer per 1,000** (from 18 fewer to 6 fewer)	⨁⨁⨁◯ MODERATE	
							-	3.7%		**13 fewer per 1,000** (from 18 fewer to 6 fewer)		

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

Explanations

a. Some concern due to imbalances on the administration of antivirals and steroids
b. Wide confidence interval with possibility for benefit and harm.
c. Heterogeneity: I2=67%

Appendix 3: Forest Plots

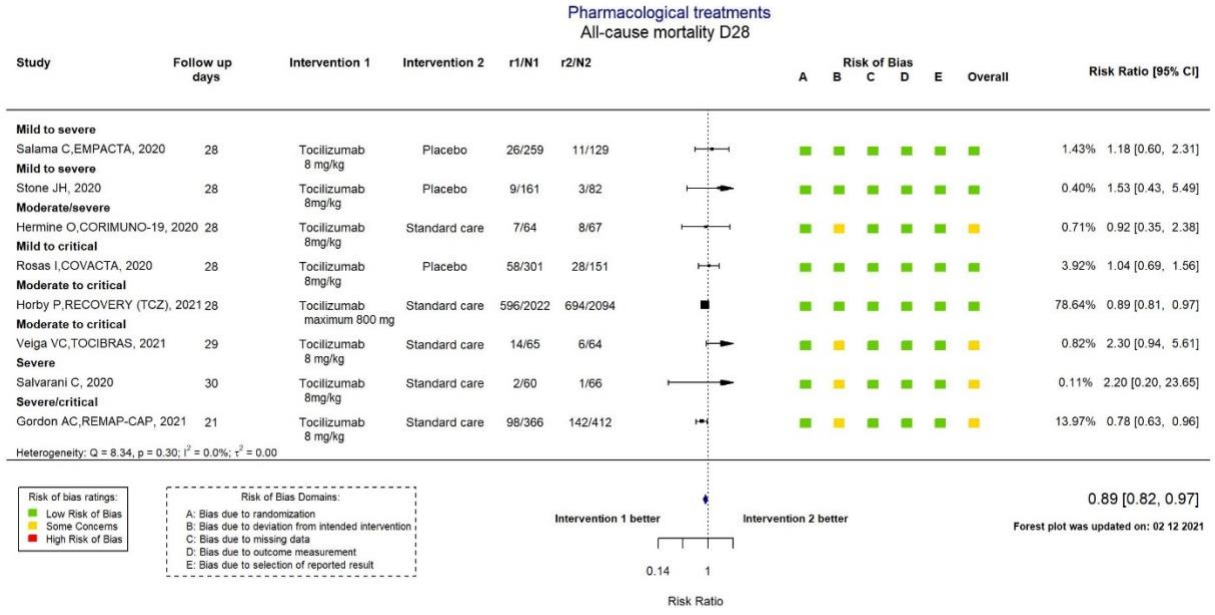

Figure 1. Pooled effect of tocilizumab on all-cause mortality at D28. Source: covid-nma.com

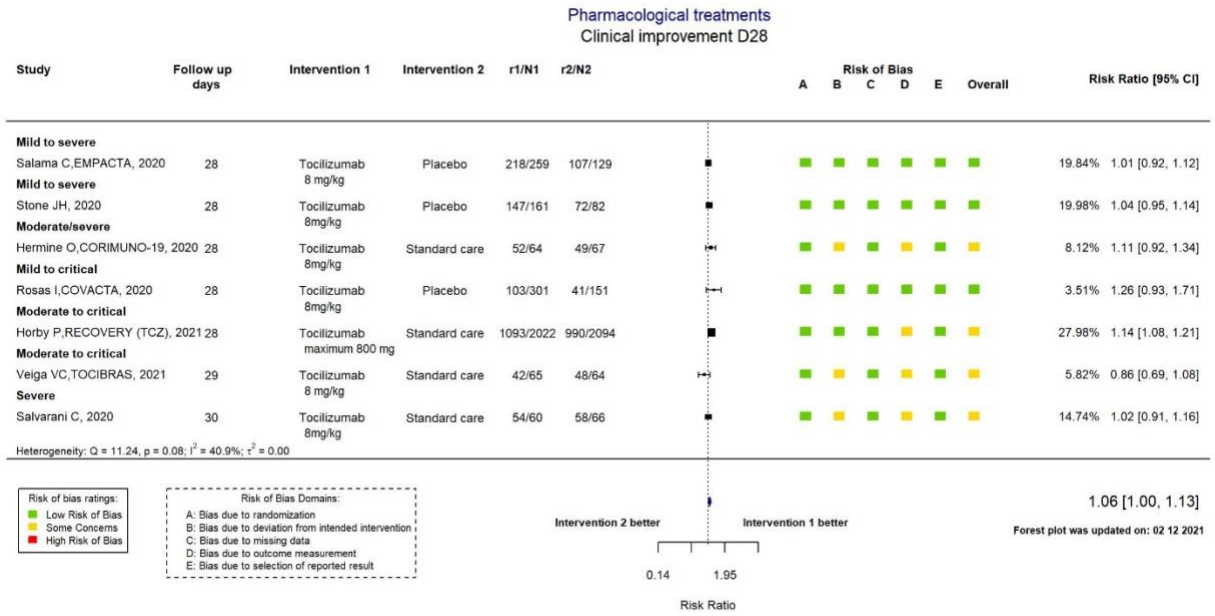

Figure 2. Pooled effect of tocilizumab on clinical improvement at day 28. Source: covid-nma.com

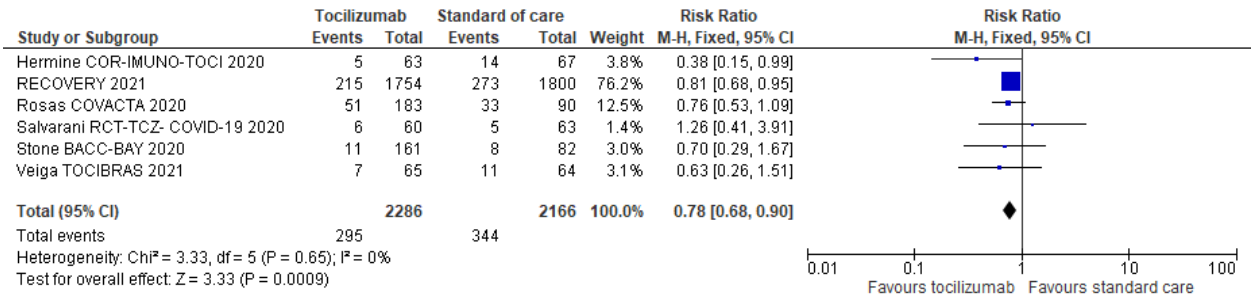

Figure 3. Pooled effect of tocilizumab on initiation of mechanical ventilation

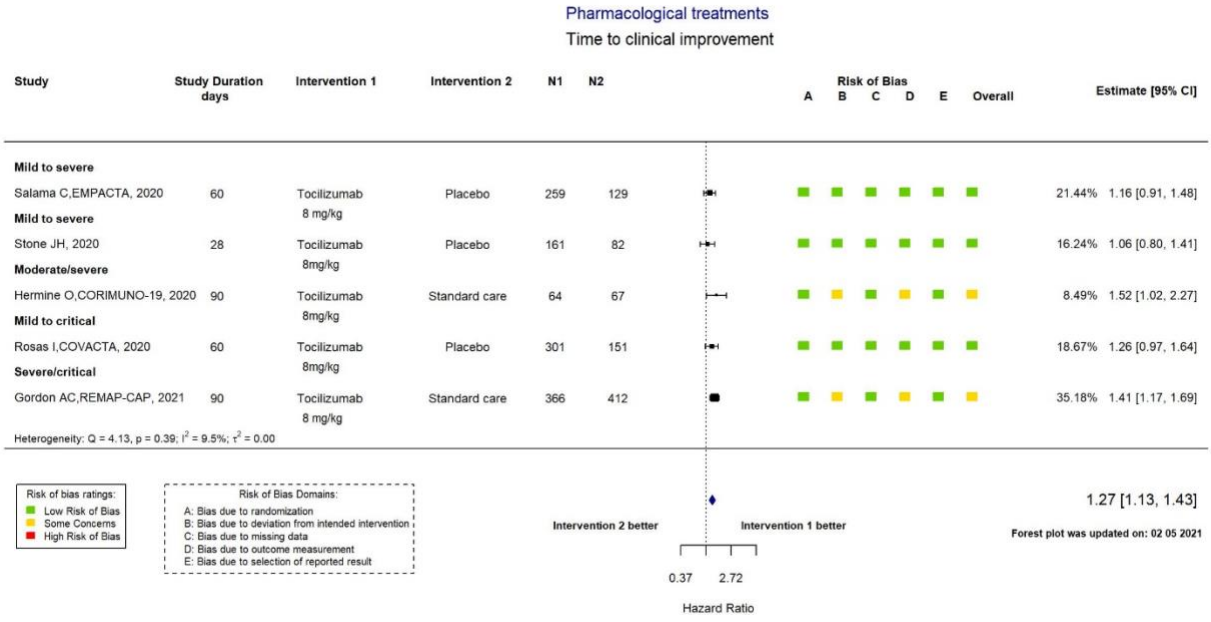

Figure 4. Pooled effect of tocilizumab on time to clinical improvement (Hazard ratio)

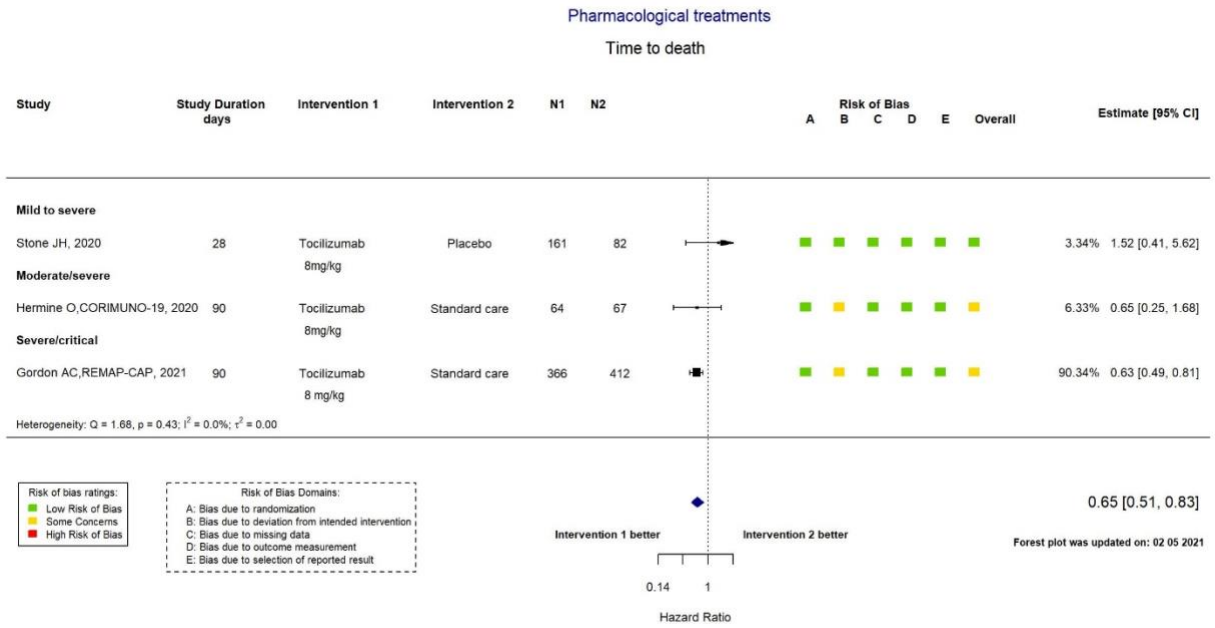

Figure 5. Pooled effect of tocilizumab on time to death (Hazard ratio)

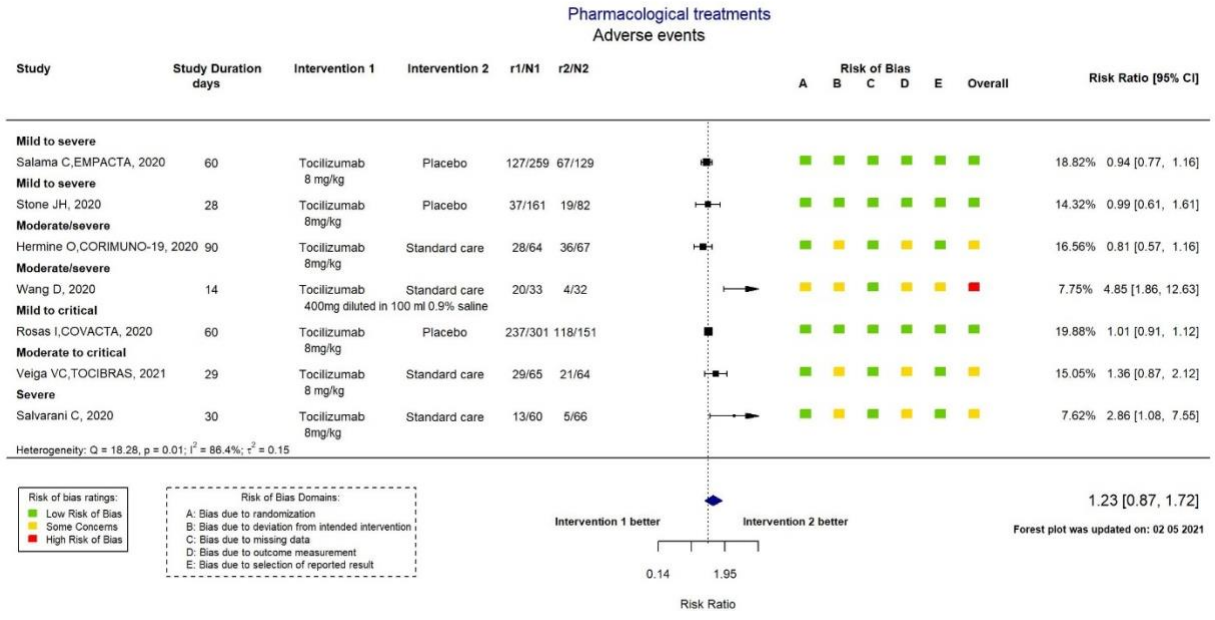

Figure 6. Pooled effect of tocilizumab on the incidence adverse event

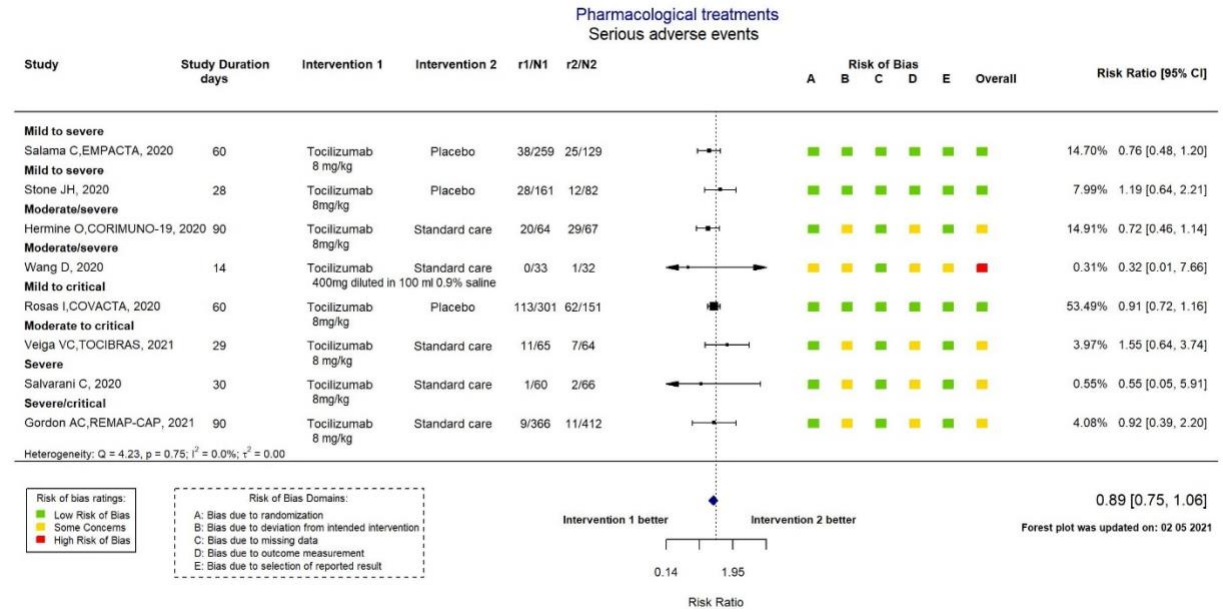

Figure 7. Pooled effect of tocilizumab on the incidence of serious adverse events

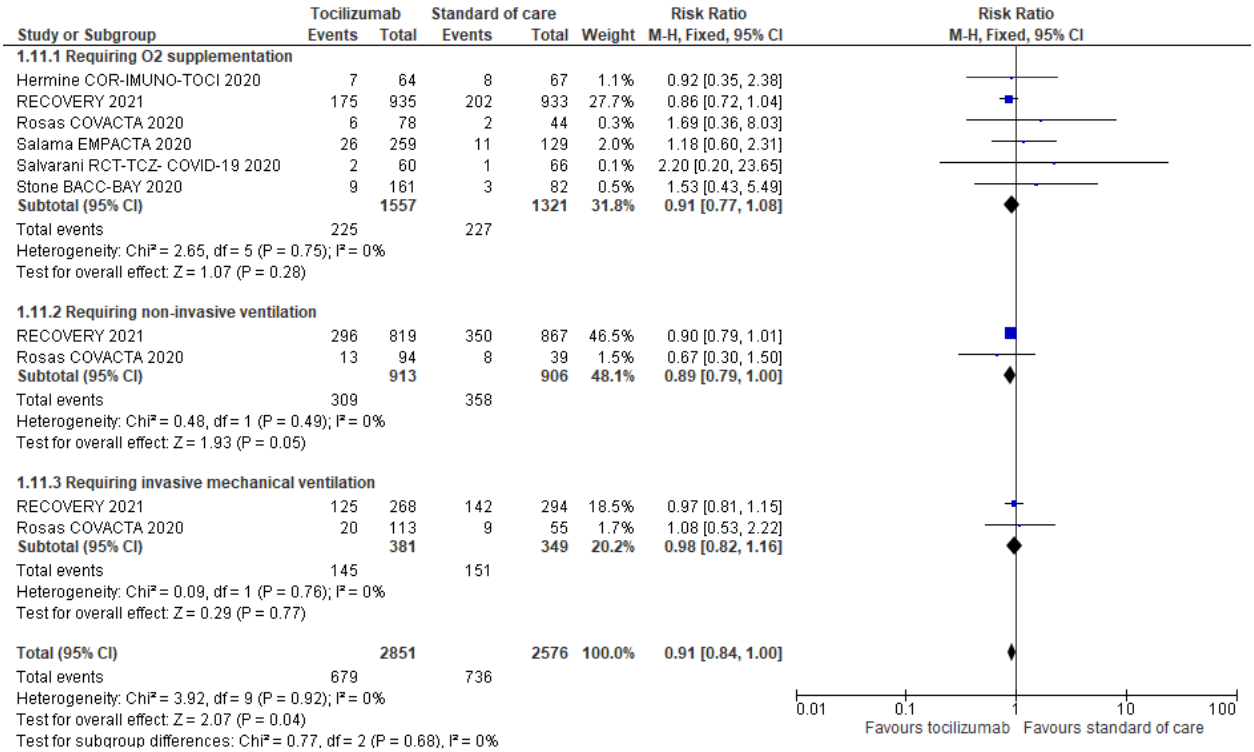

Figure 8. Pooled effect of tocilizumab on mortality according to severity

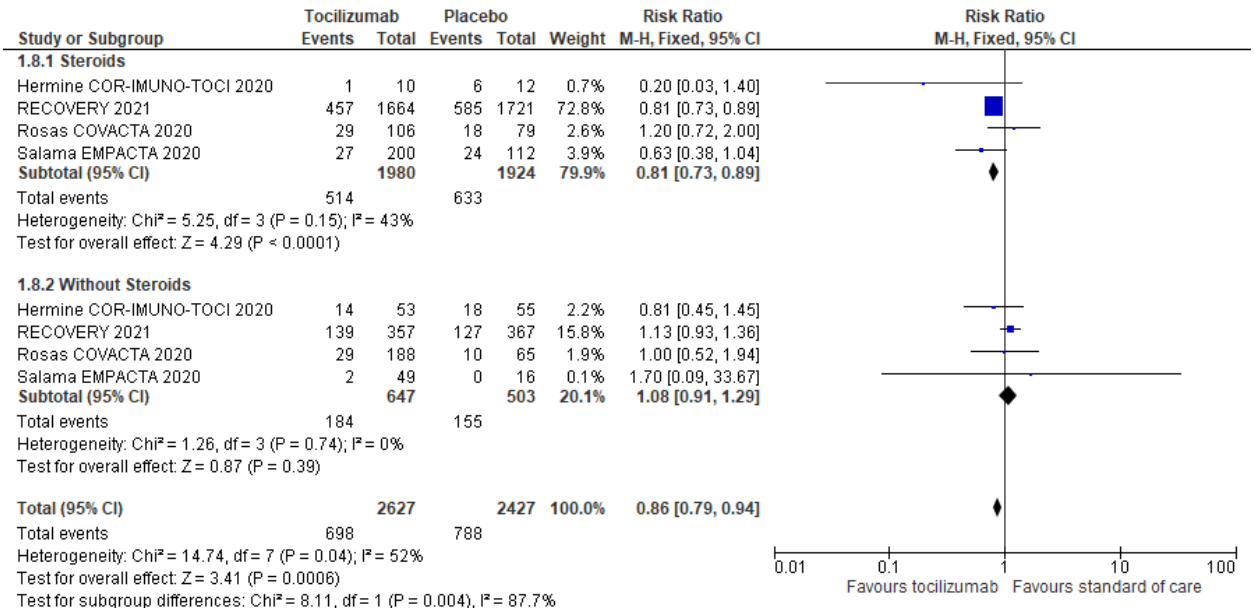

Figure 9. Pooled effect of tocilizumab on mortality with and without co-administration of steroids

Appendix 4. Pooled results of trials

Outcome	Pooled Relative Risk	95% CI	Certainty of evidence (GRADE)
All-cause mortality D28 (8 RCTs, N= 6,363)	0.89	0.82 to 0.97	Moderate
Clinical improvement D28 (7 RCTs, N= 5,585)	1.06	1.00 to 1.13	Moderate
Initiation of mechanical ventilation (6 RCTs, N=4,452)	0.78	0.68 to 0.90	Moderate
Time to clinical improvement (Hazard ratio) (7 RCTs, N= 5,585)	1.27	1.13 to 1.43	Moderate
Time to death (Hazard ratio) (3 RCTs, N = 1,152)	0.65	0.51 to 0.83	Moderate
Adverse events (7 RCTs, N=1,534)	1.23	0.87 to 1.72	Low
Serious adverse events (8 RCTs, n = 2,285)	0.89	0.75 to 1.06	Moderate

Appendix 5. Subgroup analysis

	Pooled Relative Risk	95% CI
By severity of disease		
Requiring O2 supplementation (6 RCTs, n = 2,878)	0.91	0.77 to 1.08
Requiring non-invasive ventilation (2 RCTs, n = 1,819)	0.89	0.79 to 1.00
Requiring mechanical ventilation (2 RCTs, n = 730)	0.98	0.82 to 1.16
By co-administration with steroids		
With steroids (4 RCTs, n = 5,051)	0.81	0.73 to 0.89
Without steroids (4 RCTs, n = 1,489)	1.08	0.91 to 1.29