

ACTA BIOMEDICA

REVIEWS/FOCUS ON

Acta Biomed 2022; Vol. 93, N. 1: e2022014 DOI: 10.23750/abm.v93i1.12208

Tocilizumab in addition to standard of care in the management of COVID-19: a metaanalysis of RCTs

Victor Mutua¹, Brandon Michael Henry², Chris von Csefalvay³, Isaac Cheruiyot¹, Jens Vikse⁴, Giuseppe Lippi^{5*}, Brian Bundi¹, Newnex Mong'are¹

¹School of Medicine, University of Nairobi; ²Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; ³Starschema Inc., Office of Intramural Research, Arlington, VA, USA; ⁴Department of Rheumatology, Stavanger University Hospital, Stavanger, Norway; ⁵Section of Clinical Biochemistry, University of Verona, Verona, Italy. *Prof. Giuseppe Lippi is a senior author in this paper

SUPPLEMENTARY FILES

Table 1: Summary on use of steroids and mechanical ventilation

Study	Use of corticost	eroids, n (%)	Use of Mechanical ventilation, n (%)			
	TCZ	SOC	TCZ	SOC		
(Salvarani et al.,	NA	NA	0	0		
2021)						
(Salama et al.,	200 (80.3)	112 (87.5)	0	0		
2021)						
(Hermine et al.,	21 (33)	41 (61)	0	0		
2021)						
(Rosas et al., 2021)	57 (19.4)	41 (28.5)	111 (37.8)	54 (37.5)		
(Soin et al., 2021)	(85)	(89)	5 (10)	5 (10)		
(Stone et al., 2020)	18 (11)	5 (6)	0	1 (1)		
(Veiga et al., 2021)	45 (69)	47 (73)	11 (17)	10 (16)		
(Gordon et al.,	50 (14.2)	52 (12.9)	104 (29)	121 (30)		
2021)						
(Horby et al., 2021)	1664 (82)	1721 (82)	268 (13)	294 (14)		

^{*}Corresponding author: vicmutua3@gmail.com

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Gordon et al., 2021	•	•	•	•	•	•
Hermine et al., 2021	•	•	•	•	•	•
Horby et al., 2021	•	•	•	•	•	•
Rosas et al., 2021	•	•	•	•	•	•
Salama et al., 2021	•	•	•	•	•	•
Salvarani et al., 2021	•	•	•	•	•	•
Soin et al., 2021	•	•		•	•	•
Stone et al., 2020	•	•	•	•	•	•
Veiga et al., 2021	•	•			•	•

Figure 1: Risk of bias summary

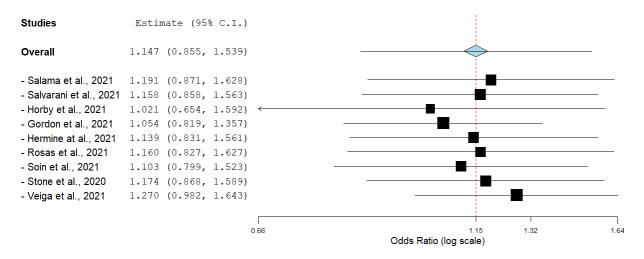


Figure 2: Leave-one-out forest plot

	Tocilizu	mab	Standard o	f care		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.1.1 Severe disease							
Gordon et al., 2021	98	353	142	402	23.6%	0.70 [0.52, 0.96]	
Horby et al., 2021	621	2022	729	2094	36.2%	0.83 [0.73, 0.95]	■
Rosas et al., 2021	58	294	28	144	14.0%	1.02 [0.62, 1.68]	+
Soin et al., 2021	8	50	14	41	4.8%	0.37 [0.14, 0.99]	
Veiga et al., 2021	14	65	6	64	4.5%	2.65 [0.95, 7.42]	
Subtotal (95% CI)		2784		2745	83.2%	0.84 [0.63, 1.12]	•
Total events	799		919				
Heterogeneity: Tau² = 0	.05; Chi² =	= 9.20, d	f = 4 (P = 0.0)	06); I² = 5	7%		
Test for overall effect: Z	= 1.21 (P	= 0.23)					
1.1.2 Non-severe disea	ise						
Hermine et al., 2021	7	63	8	67	4.2%	0.92 [0.31, 2.71]	
Salama et al., 2021	26	249	11	128	7.9%	1.24 [0.59, 2.60]	
Salvarani et al., 2021	2	60	1	63	0.9%	2.14 [0.19, 24.21]	
Soin et al., 2021	3	41	1	47	1.0%	3.63 [0.36, 36.35]	-
Stone et al., 2020	9	161	3	82	2.8%	1.56 [0.41, 5.92]	
Subtotal (95% CI)		574		387	16.8%	1.30 [0.77, 2.20]	*
Total events	47		24				
Heterogeneity: Tau² = 0	.00; Chi²=	= 1.40, d	f = 4 (P = 0.8)	$(34); I^2 = 0$	%		
Test for overall effect: Z	= 0.97 (P	= 0.33)					
Total (95% CI)		3358		3132	100.0%	0.90 [0.71, 1.13]	•
Total events	846		943				
Heterogeneity: Tau ² = 0	.03; Chi ² =	= 13.36,	df = 9 (P = 0)	.15); l² =	33%		
Test for overall effect: Z	= 0.90 (P	= 0.37)	,				0.01 0.1 1 10 100 Favours [TCZ + SOC] Favours [SOC]
Test for subgroup differ	ences: Cl	hi² = 2.0:	5, df = 1 (P =	0.15), I ²	= 51.3%		Favours [102 + 300] Favours [300]

Figure 3: Subgroup analysis for mortality based on severity of disease

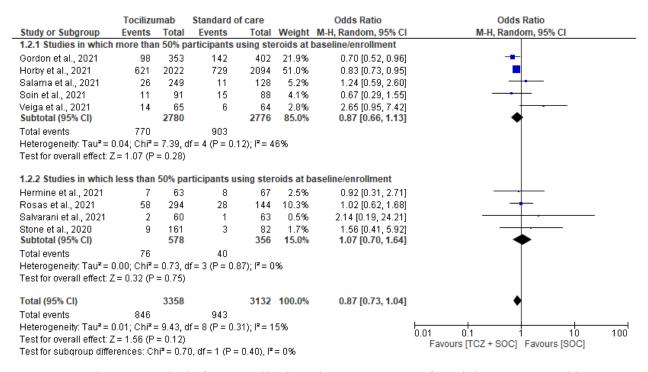


Figure 4: Subgroup analysis for mortality based on percentage of participants on steroid use at enrollment

	Tocilizu	mab	Standard o	f care		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.3.1 Studies that incl	uded MV p	atients	at enrollem	ent			
Gordon et al., 2021	98	353	142	402	25.3%	0.70 [0.52, 0.96]	-
Horby et al., 2021	621	2022	729	2094	49.6%	0.83 [0.73, 0.95]	■
Rosas et al., 2021	58	294	28	144	12.8%	1.02 [0.62, 1.68]	+
Soin et al., 2021	11	91	15	88	5.3%	0.67 [0.29, 1.55]	+
Veiga et al., 2021 Subtotal (95% CI)	14	65 2825	6	64 2792	3.6% 96.7%	2.65 [0.95, 7.42] 0.85 [0.67, 1.08]	
Total events	802		920				
Heterogeneity: Tau² = 1 Test for overall effect: 2			ff= 4 (P = 0.1	14); I² = 4	2%		
1.3.2 Studies that did	not include	e MV pa	tients at eni	rollment			
Hermine et al., 2021	7	63	8	67	3.3%	0.92 [0.31, 2.71]	
Salama et al., 2021	26	249	0	0		Not estimable	
Salvarani et al., 2021	0	0	0	0		Not estimable	
Stone et al., 2020 Subtotal (95% CI)	0	0 312	0	0 67	3.3%	Not estimable 0.92 [0.31, 2.71]	
Total events	33		8				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z= 0.15 (P	= 0.88)					
Total (95% CI)		3137		2859	100.0%	0.85 [0.69, 1.04]	•
Total events	835		928				
Heterogeneity: Tau ² = I	0.02; Chi² :	= 6.93, 0	f = 5 (P = 0.3)	23); l² = 2	8%		0.01 0.1 1 10 100
Test for overall effect: Z = 1.62 (P = 0.10)							Favours [TCZ + SOC] Favours [SOC]
Test for subgroup diffe	rences: Cl	hi² = 0.0	2. df = 1 (P =	0.89), 12	= 0%		ravours [102 · 000] Pavours [000]

Figure 5: Subgroup analysis for mortality based on use of Mechanical ventilation (MV) at enrollment.

	Tocilizu	mab	Standard o	f care		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Gordon et al., 2021	100	242	144	273	23.2%	0.63 [0.44, 0.89]	
Hermine et al., 2021	11	63	18	67	5.6%	0.58 [0.25, 1.34]	
Horby et al., 2021	619	1754	754	1800	51.8%	0.76 [0.66, 0.87]	■
Salama et al., 2021	30	249	12	128	7.7%	1.32 [0.65, 2.68]	
Stone et al., 2020	17	161	10	82	5.8%	0.85 [0.37, 1.95]	
Veiga et al., 2021	18	65	13	64	5.9%	1.50 [0.66, 3.40]	+-
Total (95% CI)		2534		2414	100.0%	0.78 [0.63, 0.96]	◆
Total events	795		951				
Heterogeneity: Tau ^z = 1	0.02; Chi²	= 6.63,	df = 5 (P = 0.	25); l² = 3		0.01 0.1 1 10 100	
Test for overall effect: 2	Z = 2.31 (P	= 0.02)				0.01 0.1 1 10 100 Favours [TCZ + SOC] Favours [SOC]	

Figure 6: Forest plot for progression to mechanical ventilation or death