Recent Clinical Data on Use of Tocilizumab for COVID-19

Updated 6/19/2020

MV= mechanical ventilation; SOC= standard of care; CRP= C-reactive protein; rec=received; SQ= subcutaneous; NC=nasal cannula; lpv/rtv= lopinavir/ritonavir; HCQ= hydroxychloroquine

Reference	Overall Findings	Limitations	Study Design	# of Patients	Treatment Regimen(s)	Severity of Illness (as reported)	Location	Outcomes	Comments
Published (peer-reviewed)									
Alattar et al.[1]	• Changes at days 1, 3, and 7 after Toci: ○ Median temp: 38, 37.3, & 37 ○ CRP: 193, 7.9, & <6 • Radiographic improvement in 44% & 68% at days 7 & 14 • Proportion of ventilated patients 84% to 60% at day 7 and 28% on day 14	Not comparative Small sample size	Retrospective review	25	All pts received 400 mg IV x 1 1 received 600 mg for 2 subsequent doses 8 total rec subsequent doses	Severe	Qatar	Toci resulted in rapid decline of inflammatory markers, reduction in vent requirement	One patient had reactivation of oral HSV
Capra et al. [2]	• HR for death 0.035, (95% CI 0.004 to 0.347); p=0.004 • Mortality: 2/62 (8%) in Toci group vs 11/23 (57.9%) • Only reviewed pts who received Toci in first 4 days after admission	Not randomized, observational, historical controls	Non-randomized, cohort	85 total, 23 before Toci available, then 62 after excluded those who received Toci after day 4 of hospitalization	SOC: (23) rec hcq, lpv/rtv, essentially a historical cohort vs Toci: (62) within 4 days of admission 800 mg IV: 2 pts 400 mg IV: 33 pts 324 mg SQ: 27 pts	RR ≥ 30 breaths/min, O_2 saturation ≤ 93%, or PaO2/FiO2<=300 mmHg Excluded those with respiratory failure at the beginning	Italy	92% of the Toci group recovered Respiratory function improved in 64.8% of Toci; all control pts worsened	No secondary infections reported, and no increase in procalcitonin

Xu et al.[3]	• By Day 5 after the Toci: (mean) ○ Lymph % normalized (15.52 --> 22.62) ○ CRP 75 → 2.72 ○ No improvement in IL-6	No control group Small sample size	Single center observation study	21	Toci (400 mg IV) after a week of SOC	Severe and critical	Shanghai, China	Clinical outcomes: Body temp returned to normal on day 1 Periph O_2 sat improved remarkably, reduced O_2 requirement CT scans showed lesions absorbed in 90.5% of patients	No emerging bacterial, fungal or viral infections were observed
Luo et al. [4]	• CRP dropped after Toci (126 to 11.2 mg/L, p<0.01) • Higher CRP at baseline associated with death, seen in 4 pts (CRP >125)	Single center Confounders and heterogeneity such as steroids Differing doses of Toci	Retrospective case series	15 pts	Toci ranged from 80 mg to 600 mg per dose, some received 6 doses 8 pts received methylpred	2 moderate 6 serious 7 critically ill	Wuhan, China	IL-6 was elevated in all, but it continued to increase to unmeasurable levels in those that died, while in others it plateaued and started declining after a week	No comment on antibiotics or secondary infections
Toniati et al[5]	• 24-72 hrs after Toci, 58 showed rapid improvement of resp and clinical condition, 37 stabilized, 5 worsened (4/5 died) • At 10 days, 77 improved, 23 worsened (20/23 died) • All had high levels of CRP, ferritin, IL-6, fibrinogen & lymphopenia. In 10 days CRP, fibrinogen, ferritin decreased toward normal D-dimer & IL-6 remained high	No control group Single center	Single center, prospective case series of COVID pneumonia and ARDS on MV	100 consecutive pts Excluded suspected or confirmed bacterial infection, active diverticulitis, GI perforation, neutropenia and thrombocytope-nia	Toci 8mg/kg x 2 doses q12h Optional 3rd dose based on clinical response, indication to give based on rapid progressive respiratory failure refractory to pharmacologic and vent support	All receiving MV or non-invasive ventilation	Brescia, Italy	All patients had lab characteristics of HIS (hyperinflam syndrome)	One patient had GI perforation requiring surgery and was alive at day 10

Sciasca et al.[6]	• Observed improvement in ferritin, CRP, D-dimer, and lymphocyte counts. • Pa02/FI02 improved (mean 152 decreased to 284 by day 7) • Use of Toci w/in 6 days of admission was assoc with increased survival (HR 2.2 95% CI 1.3-6.7, p< 0.05)	No control arm Route varied, dose for SQ was based on PK analysis in RA patients	Pilot prospective open, single arm multicenter	63	34 received 8mg/kg IV, 29 received 324mg SQ 52 patients received a second dose	Severe but also at least 3 of the following: • CRP 10 x normal • Ferritin >1000 • D-dimer >10x normal • LDH >2x normal	Torina, Italy	D-dimer levels at baseline (HR 5.01; 95% CI: 1.04-29.17) but no baseline IL-6 levels were predictors of death.	No details on secondary infections
Pre-print (non-peer reviewed)									
CORIMUNO-TOCI trial **(prelim press release)**	• Proportion of participants who had died or needed MV or noninvasive vent was lower in the Toci group		Open-label, randomized trial of hosp pts	129	65 Toci (8mg/kg) on day 1 then 2nd dose on day 3 if no response to 1st dose	Moderate or severe	7 sites in France		
Martinez-Sanz et al.[7]	• Toci assoc w/ decreased death aHR 0.34, (95% CI=0.16-0.72, p=0.005) and ICU admission or death aHR 0.38, 95% CI=0.19-0.81, p=0.011) in those with baseline CRP >150mg/L, but not <151		Observational Cohort study	1,229 pts	Median total dose of 600mg (IQR 600-800mg) admin at median of hospital day 4		17 hospitals in Spain	Time to death and time to ICU admission	
Rossi et al. [8]	• Overall 71 deaths (28.9%), propensity matched cohorts Toci associated w/ lower primary composite outcome (HR 0.49, 95%CI=0.3-0.81, p=0.005), Cox multivar analysis aHR = 0.26 (95%CI=0.135-0.51, p=0.0001)	Retrospective, single center, treatment per clinician	Retrospective case-control	246 total, 106 treated w/ Toci	400mg IV single dose, given at median day 8.4	SpO2 <96% despite NC O_2 support >6L/min for more than 6 hours, excluded ICU pts and MV pts	France	Composite of mortality and ventilation	
Petrak et al. [9]	• Any MV based on days since admission- each day of delay increases odds of requiring MV by 21% • Mortality was 13.5% vs 68.2% in early vs. late Toci groups (p<0.001)	No control group	Observational cohort	145	123 single dose Toci 22 received two doses Toci doses: • 4 mg/kg up to 400 mg, n=135	56% received MV	24 US Hospitals served by Metro ID		Primary outcome was mortality in early vs late. However, the primary analysis was only

					• 600 mg, n=5 • 800 mg, n=4 "Early": Toci within 1 day of MV, or admission if no MV "Late": Toci >1 day after intubation				conducted in 81 patients who required MV (37 early, 44 late)
Moreno-Garcia et al. [10]	• Fewer Toci patients transferred to the ICU (10.3% vs 27.6%, p=0.005)			171 pts not requiring ICU in first 24 hours. 77 received Toci	SOC: lpv/rtv, + HCQ + azithro (after 3/18) Tx: Toci criteria were progressive respiratory failure, CRP $\geq$ 8, ferritin $\geq$ 800, & lymphocyte count < 800, but ultimately left to decision of attending physician				Toci group had higher baseline CRP and O_2 requirement
Formina et al. [11]	• NEWS2 scores dropped from 5 to 2 among non-MV pts, CRP dropped from 89 to 35			89, but analysis performed in 72 pts not MV	400mg IV, 74 of them also rec HCQ, azithro, and lpv/rtv		Moscow, Russia	Overall mortality associated with very high CRP (>30mg/L) (diff not significant) and low lymphocyte counts at baseline	

Somers et al.[12]	• Toci was associated with lower risk of death in adjusted model, HR ratio 0.55 (95% CI 0.33, 0.90)] and improved status on ordinal outcome scale [OR per 1-level increase: 0.59 (0.36, 0.95)] • But more superinfections (54% vs 26%, p<0.001)	Single center	Observational Cohort (Registry)	154 MV patients	SOC: 76 Toci: 78 Toci dosed as 8 mg/kg up to 800 mg, x1 dose mostly (74%) within 24 h of intubation		Ann Arbor, Michigan		Toci group were younger and less likely to have chronic pulm disease
Ramaswamy et al.[13]	• Unadjusted mortality was 14.3% in Toci group vs 12.3% in control group. However, reported lower risk of mortality in a Cox proportional hazard model (75% reduction, HR 0.25,; 95% CI 0.07 – 0.90	Small sample size, selection bias, and retrospective data analysis	Case control, observational	21	400mg IV (14), or 8mg/kg up to 800mg		NC - US (Cone Health)	HR should be interpreted with caution, and the large confidence interval around it are representative of uncertainty that might occur with a small sample size	Prescribers chose to use tocilizumab in patients displaying more severe illness at a relatively late time point in the course of disease, but it is this group of patients that was found to have a lower risk of short-term mortality
Rimland et al.[14]	• Median CRP prior was 221 vs 19.7mg/L after (p=0.001)	Retrospective, lack of control group, small sample size, selection bias, and potential lack of generalizability since it is a single center experience	Case series	11	Toci median dose 7.9 mg/kg (IQR 5.8 – 8.1), at median time to admin of hospital day 1, and 9 days after onset of symptoms	9/11 critically ill requiring ICU admission and mechanical ventilation; severe or critical by modified WHO criteria	Chapel Hill, NC - US (UNC)	There was no evidence of improvements in oxygen requirement, temperature, other markers of severe disease, or clinical outcomes in this cohort.	Baseline IL-6 not available

Wadud et al.[15]	• There was a higher HS score in Toci group (114 vs. 92) - although the preprint lacks data tables that allow you to view study population characteristics • Higher survival in Toci group (61.36% vs 48%, p<0.00001)	Retrospective study, unable to control for many confounders for mortality	Retrospective case-control. Patients were matched on: age, sex, BMI, and HS score	94 total, 44 in Toci group and 50 in control 84% males	Not reported		Orange Regional Medical Center, New York	*"If we treat 8 patients with tocilizumab, 1 will not die"*	HS score = calculated using inflammatory markers- ferritin, triglycerides, AST and fibrinogen

References:

1. Alattar R, Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *Journal of Medical Virology*. n/a(n/a).
2. Capra R, De Rossi N, Mattioli F, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *European Journal of Internal Medicine*. 2020;76:31-35.
3. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *PNAS*. 2020;117(20):10970-10975.
4. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol*. Published online April 15, 2020.
5. Toniati P, Piva S, Cattalini M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. *Autoimmun Rev*. 2020;19(7):102568.
6. Sciascia S, Aprà F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol*. 2020;38(3):529-532.
7. Martinez-Sanz J, Muriel A, Ron R, et al. Effects of Tocilizumab on Mortality in Hospitalized Patients with COVID-19: A Multicenter Cohort Study. *medRxiv*. Published online June 9, 2020:2020.06.08.20125245.
8. Rossi B, Nguyen LS, Zimmermann P, et al. Effect of tocilizumab in hospitalized patients with severe pneumonia COVID-19: a cohort study. *medRxiv*. Published online June 9, 2020:2020.06.06.20122341.
9. Petrak R, Skorodin N, Hise NV, et al. Tocilizumab as a Therapeutic Agent for Critically Ill Patients Infected with SARS-CoV-2. *medRxiv*. Published online June 8, 2020:2020.06.05.20122622.
10. Moreno Garcia E, Rico Caballero V, Albiach L, et al. *Tocilizumab Is Associated with Reduction of the Risk of ICU Admission and Mortality in Patients with SARS-CoV-2 Infection*. Infectious Diseases (except HIV/AIDS); 2020.
11. Formina DS, Lysenko MA, Beloglazova IP, et al. Temporal clinical and laboratory response to interleukin-6 receptor blockade with Tocilizumab in 89 hospitalized patients with COVID-19 pneumonia. *medRxiv*. Published online June 12, 2020:2020.06.12.20122374.
12. Somers EC, Eschenauer GA, Troost JP, et al. *Tocilizumab for Treatment of Mechanically Ventilated Patients with COVID-19*. Infectious Diseases (except HIV/AIDS). *medRxiv*. Published online June 3, 2020:2020.05.29.20117358.
13. Ramaswamy M, Mannam P, Comer R, Sinclair E, McQuaid DB, Schmidt ML. Off-Label Real World Experience Using Tocilizumab for Patients Hospitalized with COVID-19 Disease in a Regional Community Health System: A Case-Control Study. medRxiv. Published online May 19 2020:2020.05.14.20099234.
14. Rimland CA, Morgan CE, Bell GJ, et al. Clinical characteristics and early outcomes in patients with COVID-19 treated with tocilizumab at a United States academic center. *medRxiv*. Published online May 19, 2020:2020.05.13.20100404.
15. Wadud N, Ahmed N, Shergil MM, et al. Improved survival outcome in SARs-CoV-2 (COVID-19) Acute Respiratory Distress Syndrome patients with Tocilizumab administration. *medRxiv*. Published online May 16, 2020:2020.05.13.20100081.