Tocilizumab (Actemra®) & Other IL-6 Antagonists

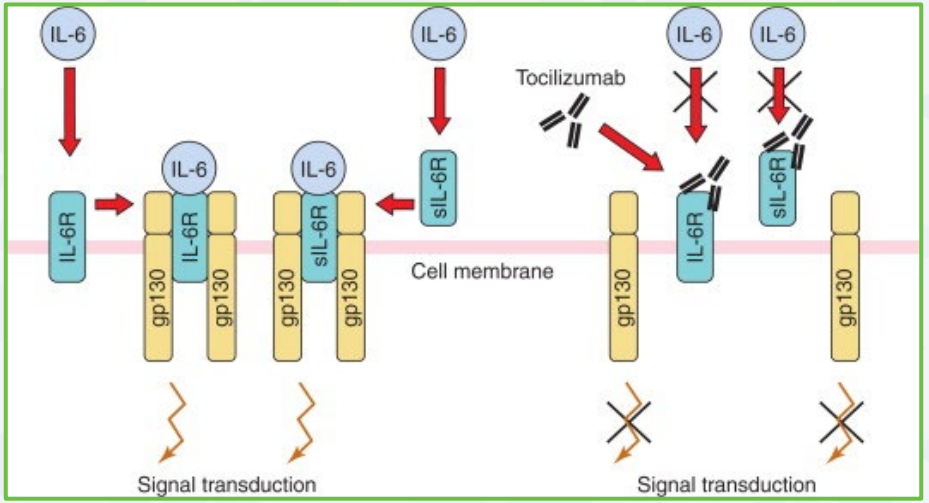
An Updated Review of Pertinent Drug Information for SARS-CoV-2

Ana D. Vega, PharmD, BCIDP
Jackson Memorial Hospital
ana.vega@jhsmiami.org
@microbepharmd
November 6, 2020

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Mechanism of Action

- Tocilizumab is a humanized monoclonal antibody against human IL-6 receptor (IL-6R)
- Binds to membrane-bound and soluble forms of IL-6R
- Competitively inhibits IL-6 to IL-6R thereby inhibiting signal transduction[1]
- Pathogenesis of previous coronaviruses (SARS, MERS) suggests a cytokine storm is involved.[2,3]



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

1. Nishimoto N, Mima T. *Rheumatoid Arthritis*. 2009; 10J:367.
2. Li Y, Chen M, Cao H, et al. *Microbes Infect* 2013;**15**:88-95.
3. Lau SK, Lau CC, Chan KH, et al. *J Gen Virol* 2013;**94**:2679-90.

Tocilizumab Case Reports

Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure[1]

- 42 year old man, diagnosed with metastatic sarcomatoid clear cell renal cell carcinoma
- Day 1: admitted for fever, symptomatic bone metastases
- Day 6: cough and fever; SARS-CoV-2 positive
- Day 7: lopinavir-ritonavir (400 mg-100 mg) and piperacillin/tazobactam initiated
- Day 8: desaturation requiring 6L/min supplemental oxygen, CRP 225 mg/dL
  - 2 doses of Tocilizumab 8 mg/kg, 8 hours apart
- Day 12: supplemental oxygen discontinued, improvement in CT chest, afebrile (occurred "rapidly" after TCZ), CRP 33 mg/dL

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

1. Michot JM, Albiges L, Chaput N, et al. *Annals of Oncology 2020*. https://doi.org/10.1016/j.annonc.2020.03.300.

Tocilizumab Case Reports

First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab[1]

- 60 year old man working in Wuhan, China admitted for chest tightness with CT chest demonstrating multiple GGO and pneumatocele bilaterally; SARS-CoV-2 positive
  - Treated with moxifloxacin 400 mg IV daily x 3 days and umifenovir 200 mg 3 times daily
- PMH: multiple myeloma diagnosed 5/2015, with clinical recovery after two cycles of induction chemotherapy and maintenance therapy with thalidomide
- Day 15: patient is readmitted with dyspnea and desaturation (~93% SpO2 at rest); MP x 5 days
- Day 24: chest tightness and CT lesions persisted; Tocilizumab 8 mg/kg IV x 1 administered
- Day 27: chest tightness resolved
- Day 34: 3rd CT chest now with improvement in lesions; patient discharged

GGO: ground-glass opacities; MP: methylprednisolone

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

1. Zhang X, Song K, Tong F, et al. *Blood Advances* 2020; 4(7): 1307-1310. doi:10.1182/bloodadvances.2020001907

Tocilizumab Case Reports

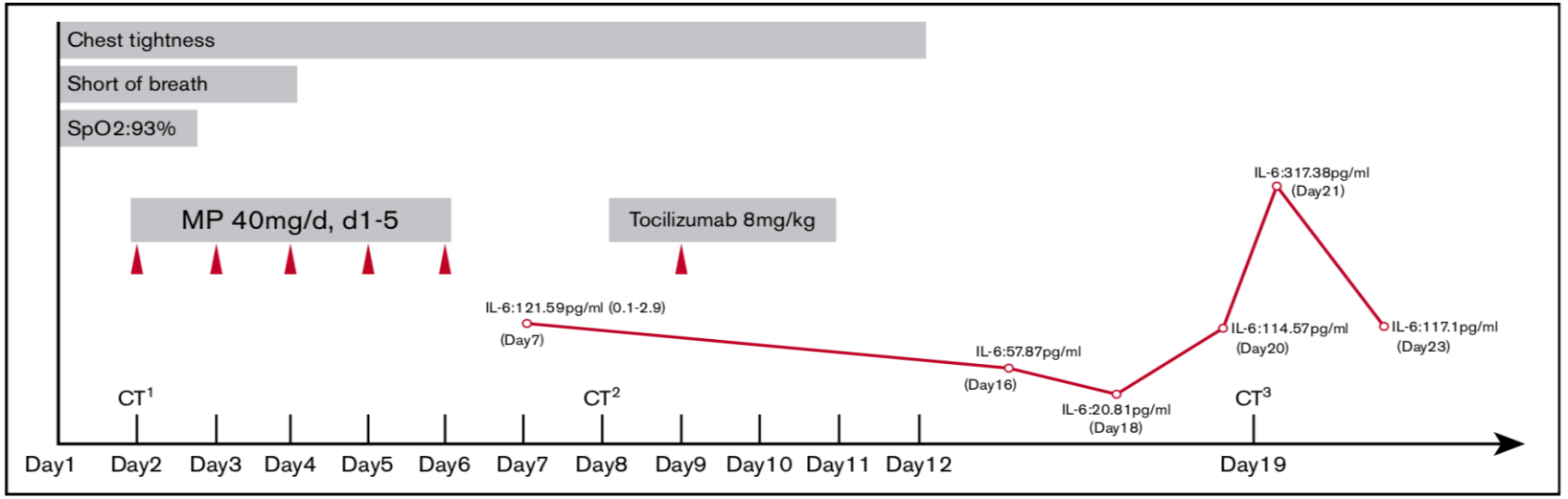


Figure 2. Timeline of symptoms, IL-6 level, and treatment after admission. CT^1, first CT scan; CT^2, second CT scan; CT^3, third CT scan; MP, methylprednisolone; SpO_2, peripheral oxygen saturation.

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

1. Zhang X, Song K, Tong F, et al. *Blood Advances* 2020; 4(7): 1307-1310. doi:10.1182/bloodadvances.2020001907

Tocilizumab (Cautionary) Case Reports

Case 1

- 40-year-old man with no medical history presented with 5 days of fever, dry cough, and dyspnea on exertion.
- SARS-CoV-2 confirmed by PCR
- Started on Hydroxychloroquine and azithromycin
- Hypoxemia progresses requiring mechanical ventilation two days later
- Develops ARDS and on day 4, septic shock, started on norepinephrine
- Tocilizumab 400 mg IV administered
- Next day, patient develops STEMI, diagnosed with viral myocarditis
- Following day, patient febrile to 109F and in septic shock refractory to 4 vasopressors – passes away

Case 2

- 69-year-old woman with a history of type 2 diabetes mellitus, rheumatoid arthritis, and aplastic anemia presented with 6 days of productive cough, pleuritic chest pain, fever, fatigue, and abdominal pain.
- On exam: febrile to 100.5F, saturating 95% on room air, CT chest with diffuse bilateral nodular opacities
- On hospital day 2, she rapidly progresses into respiratory failure and septic shock.
- Patient intubated, started on norepinephrine, and treated with a dose of tocilizumab (560 mg IV).
- Day 3: shock continues to worsen requiring max dose pressors
- Day 4: receives second dose of tocilizumab (700 mg IV)
- Despite second dose, patient passes away

PCR: polymerase-chain reaction; ARDS: acute respiratory distress syndrome; CT: computer tomography; STEMI: ST-segment elevation myocardial infarction

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Radbel J, Narayanan N, Bhatt Pinki. *CHEST* 2020. https://doi.org/10.1016/j.chest.2020.04.024

Tocilizumab Case Series

Purpose

To evaluate treatment response to tocilizumab in COVID-19 patients with varying disease severities* (**N = 15**)

Disease Severity

Moderately ill (n = 2)
Fever, respiratory symptoms, radiological signs of pneumonia

Severely ill (n = 6)
Any of the following:
(1) RR> 30 br/min
(2) SpO2 <93% at rest
(3) PaO2/FiO2<300 mmHg

Critically ill (n = 7)
Mechanical ventilation or shock requiring ICU care

Drug Therapy

Tocilizumab (TCZ) Dose: Ranged from 80-600 mg**

Eight patients received TCZ in combination with methylprednisolone

Other therapies (antivirals, antibiotics, supportive care) not described

Results

Median age: 73 years (62-80)

Death: 20% (n = 3)
Improvement: 6.7% (n = 1)
Stability: 60% (n = 9)
Aggravation: 13.3% (n = 2)

Baseline elevations seen in CRP and IL-6 levels returned to normal in ten and zero patients, respectively.***

Conclusions

"A single dose of TCZ seems to fail to improve the disease activity in critically ill patients…however, repeated doses might improve the condition of critically ill patients"

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

*Based on 5th edition of China Guideline for Diagnosis and Treatment of 2019-nCoV
**Five patients received 2 or more doses of TCZ.
***Normal levels defined as: CRP: ≤ 5 mg/L, IL-6 ≤ 7 pg/mL
RR: respiratory rate; ICU: intensive care unit; CRP: C-reactive protein; IL-6: interleukin-6

Luo P, Liu Y, Qiu L, et al. *J Med Virol* 2020; 1-5. doi: 10.1002/jmv.25801.

Limitations

- Patients followed for 7 days only
- Concomitant therapies not described
- Baseline characteristics missing entirely
- Fever, clinical symptoms, oxygen requirement, CT scan improvement not described
- Dosing of Tocilizumab unclear
- Adverse effects not described

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

TABLE 1 The characteristics of COVID-19 patients treated with TCZ

Case No.	Age	Sex	Clinical classification	Co-morbidity	Therapy							
					Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	73	M	Critically ill	Hypertension	TCZ 480 mg MP 40 mg	MP 40 mg	MP 40 mg	MP 40 mg	...	...	...	...
2	62	M	Critically ill	None	TCZ 600 mg MP 40 mg	MP 40 mg bid	MP 40 mg bid	MP 40 mg bid	...	...	...	...
3	62	M	Critically ill	Hypertension	TCZ 320 mg MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	...	...
4	74	M	Critically ill	Hypertension Stroke history	TCZ 480 mg	...	...	TCZ 480 mg	...	...	...	...
5	72	M	Critically ill	Hypertension	TCZ 100 mg	TCZ 240 mg	...	...	...	...	...	...
6	73	M	Critically ill	None	TCZ 80 mg	TCZ 160 mg	TCZ 80 mg	...	...	...	...	...
7	65	M	Critically ill	Hypertension Stroke history	TCZ 480 mg MP 40 mg	MP 40 mg bid	MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	MP 80 mg bid	...	...
8	66	F	Seriously ill	Stroke history	TCZ 480 mg MP 80 mg	MP 80 mg	MP 80 mg	MP 80 mg	...	...	...	...
9	73	M	Seriously ill	Hypertension Diabetes	TCZ 480 mg	...	TCZ 480 mg	...	...	...	...	...
10	77	M	Seriously ill	Hypertension Diabetes	TCZ 400 mg	...	...	...	...	...	...	...
11	65	F	Seriously ill	Hypertension Diabetes	TCZ 400 mg MP 40 mg	MP 40 mg bid	MP 40 mg bid	MP 40 mg bid	MP 40 mg	MP 40 mg	MP 40 mg	...
12	77	M	Seriously ill	Hypertension Diabetes	TCZ 400 mg	...	...	...	...	...	...	...
13	75	M	Moderately ill	None	TCZ 480 mg MP 40 mg	MP 40 mg bid	MP 40 mg bid	MP 40 mg bid	MP 40 mg bid	...	...	...
14	77	M	Moderately ill	None	TCZ 80 mg	TCZ 160 mg	TCZ 80 mg	...	...	...	...	...
15	80	F	Seriously ill	None	TCZ 240 mg MP 40 mg	MP 40 mg bid	MP 40 mg bid	MP 40 mg bid	...	...	M	M) 20 mg

Abbreviations: bid, twice a day; F, female; M, male; MP, methylprednisolone; TCZ, tocilizumab.

Luo P, Liu Y, Qiu L, et al. *J Med Virol* 2020; 1-5. doi: 10.1002/jmv.25801.

Tocilizumab Single-arm Prospective Study

Purpose

To evaluate treatment response to tocilizumab in severe COVID-19 patients across 4 centers
(**N = 63**)

Inclusion

All of the following:
(1) PCR-confirmed SARS-CoV-2 infection
(2) **SpO2** <93% on room air or **PaO2/FiO2** <300 mmHg
(3) At least 3 of the following: **CRP** > 10x normal values, **ferritin** > 1000 ng/mL, **D-dimer** > 10x normal values, **LDH** > 2x upper limit of normal

Methods

Patients received either Tocilizumab (TCZ) 8 mg/ kg IV or 324 mg SQ once*

Primary end-point: safety
Secondary end-points: improvement of respiratory and laboratory parameters

Multivariable logistic regression to identify predictors of poor prognosis

Results

- Mean age (y): 62.6 ± 12.5
- No severe/moderate ADE
- Significant decrease in mean CRP and D-dimer by day 14
- Mean PaO2/FiO2 increased significantly by day 14 (152±53 to 302.2±126)
- TCZ within 6 days of admission associated with increased likelihood of survival (HR 2.2 95%CI 1.3–6.7, p<0.05)

Conclusions

Data suggests a promising role of TCZ in terms of efficacy and highlights safety profile of TCZ for COVID-19

SIDP
SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

*52 patients received a second dose within 24h
CRP: C-reactive protein; LDH: lactate dehydrogenase; IV: intravenous; SQ: subcutaneous; LPV/r: lopinavir; DRV/c: darunavir/cobicistat; ADE: adverse drug event; HR: hazards Ratio

Sciascia S, Apra F, Baffa A, et al. *Clinical and Experimental Rheumatology* 2020; 38: 00-00.
https://www.clinexprheumatol.org/article.asp?a=15723.

Tocilizumab in the Press

Tocilizumab improves significantly clinical outcomes of patients with moderate or severe COVID-19 pneumonia

- French multicenter open-label randomized controlled trial of tocilizumab (part of CORIMUNO-19 platform)
- COVID-19 moderate or severe pneumonia not requiring intensive care upon admission
- Primary composite outcome: need for ventilation (non-invasive or mechanical) or death at day 14
- A total of 129 patients were randomized: 65 to SOC + tocilizumab; 64 to SOC alone
- A significantly lower proportion of patients reached the primary outcome in the tocilizumab arm
- Results pending publication

SOC: standard-of-care

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

https://pipelinereview.com/index.php/2020042874458/Antibodies/Tocilizumab-improves-significantly-clinical-outcomes-of-patients-with-moderate-or-severe-COVID-19-pneumonia.html

Other IL-6 Antagonists: Sarilumab (Kevzara ®) & Siltuximab (Sylvant ®)

Sarilumab

- FDA approved for rheumatoid arthritis
- Dosing: 200 mg SubQ once every 2 weeks
- Precautions: Do not initiate if ANC is <2,000/mm^3, platelets are <150,000/mm^3, or if ALT/AST >1.5 times ULN.
- U.S. Boxed Warning: risk of serious infections

Siltuximab

- FDA approved for multicentric Castleman's Disease
- Dose: 11 mg/kg IV once weekly or once every 3 weeks
- Consider delaying treatment until ANC ≥1000/mm^3, platelets ≥50,000/mm^3, and hemoglobin <17 g/dL
- Risk of infection is also a consideration with this agent

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

1. Sarilumab [package insert]. Bridgewater, NJ: sanofi-aventis U.S. LLC, Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2018.
2. Siltuximab [package insert]. Cilag AG, Schaffhausen, Switzerland: Janssen Biotech, Inc; 2018.

Data Available: Sarilumab

SANOFI

Press Release

Source: Sanofi (EURONEXT: SAN) (NASDAQ: SNY)

- Phase 2 portion compared IV Sarilumab (Kevzara) 400 mg vs 200 mg vs placebo in 457 patients:
  - Severe illness: 28% (requiring oxygen - **not** mechanical or high-flow oxygenation)
  - Critical illness 49% (requiring mechanical or high-flow oxygenation or in an ICU)
  - Multi-system organ dysfunction: 23%
  - Independent Data Monitoring Committee recommended continuing ongoing Phase 3 trial only in the **more advanced "critical" group with Sarilumab higher-dose** versus placebo and discontinuing less advanced "severe" group

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-27-12-58-00

Data Available: Sarilumab

U.S. Sarilumab Trial – Phase 2 Efficacy Results

	Placebo	Kevzara 200 mg	Kevzara 400 mg
PRIMARY ENDPOINT (REDUCTION IN C-REACTIVE PROTEIN)			
	(n=77)	*(n=136)*	*(n=145)*
% change from baseline in CRP (Patients with high baseline IL-6, where data was available)	-21%	-77%	-79%
EXPLORATORY CLINICAL ENDPOINTS IN "CRITICAL" GROUP			
	(n=44)	*(n=94)*	*(n=88)*
Died or "On a ventilator"	24 (55%)	43 (46%)	28 (32%)
Died	*12 (27%)*	*34 (36%)*	*20 (23%)*
On a ventilator	*12 (27%)*	*9 (10%)*	*8 (9%)*
Clinical improvement (Achieved ³2 point improvement on 7-point scale)[1]	18 (41%)	48 (51%)	52 (59%)
Off oxygenation	18 (41%)	40 (43%)	51 (58%)
Discharged	18 (41%)	37 (39%)	47 (53%)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-27-12-58-00

Siltuximab Case Series

Purpose

To evaluate treatment response to Siltuximab in COVID-19 patients with ARDS (**N = 21**)

Methods

All patients received standard of care (not described) and siltuximab 11 mg/kg/day IV once.

A second dose could be administered at the physician's discretion.*

Results

- Median age: 64 years (48-75)
- Median PaO2/FiO2: 127
- 100% of patients required non-invasive ventilation (NIV)
- 85.7% (n = 18) received siltuximab within 24 hours of NIV (100% within 48h)

Results

- Improvement with reduced need for NIV: 33% (n = 7)
- Stability: 43% (n = 9)
- Worsening requiring intubation or death: 24% (n = 5)

- Baseline elevations seen in CRP all returned to normal limits by day 5 (n = 16)

Conclusions

"[There is a] potential role of siltuximab in treating patients with SARS-CoV-2 infection who develop pneumonia/ARDS requiring CPAP/NIV"

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

*Five patients received a second dose.

ARDS: acute respiratory distress syndrome; CRP: C-reactive protein; CPAP: continuous positive air[illegible]essure

Gritti G, Raimondi F, Ripamonti D, et al. https://doi.org/10.1101/2020.04.01.20048561.

Relevant Clinical Trials*

Sarilumab

- Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19 (NCT04315298) – COMPLETE; did not meet primary outcome (data unpublished)
- Sarilumab for Patients With Moderate COVID-19 Disease: A Randomized Controlled Trial With a Play-The-Winner Design (NCT04359901)
- **SARCOVID**: Efficacy of Subcutaneous Sarilumab in Hospitalised Patients With Moderate-severe COVID-19 Infection (NCT04357808)

Siltuximab

- Efficacy and Safety of Siltuximab vs. Corticosteroids in Hospitalized Patients With COVID-19 Pneumonia (NCT04329650)
- **SISCO**: An Observational Case-control Study of the Use of Siltuximab in ARDS Patients Diagnosed With COVID-19 Infection (NCT04322188)
- **COV-AID**: Treatment of COVID-19 Patients With Anti-interleukin Drugs [phase 3 observational study] (NCT04330638)

Tocilizumab

- **COVACTA**: A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (NCT04320615)
- **EMPACTA:** A Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia (NCT04372186)
- **REMDACTA:** 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 (NCT04409262)
- Tocilizumab for Prevention of Respiratory Failure in Patients With Severe COVID-19 Infection (NCT04377659)
- **COVIDOSE**: Tocilizumab to Prevent Clinical Decompensation in Hospitalized, critically Ill Patients With COVID-19 Pneumonitis (NCT04331795)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

*Not all-inclusive; only included US clinical trials for Tocilizumab; only recruiting trials

Summary

- Tocilizumab, Sarilumab, and Siltuximab are humanized monoclonal antibodies against human IL-6 receptor (IL-6R)
- Since cytokine release syndrome (CRS) may be involved in the pathogenesis of SARS-CoV-2, these agents are under investigation for COVID-19
- Currently available data is mixed for Tocilizumab, with a recent single-arm prospective study demonstrating potential benefit
- Sarilumab phase 2 trial demonstrated a signal of benefit for patients with critical (but not severe) COVID-19
- More robust data on Siltuximab for COVID-19 needs to become available before conclusions can be drawn
- Safety profiles includes increased risk for infection with all 3 agents
- Randomized clinical trails are ongoing for Tocilizumab and Sarilumab in COVID-19

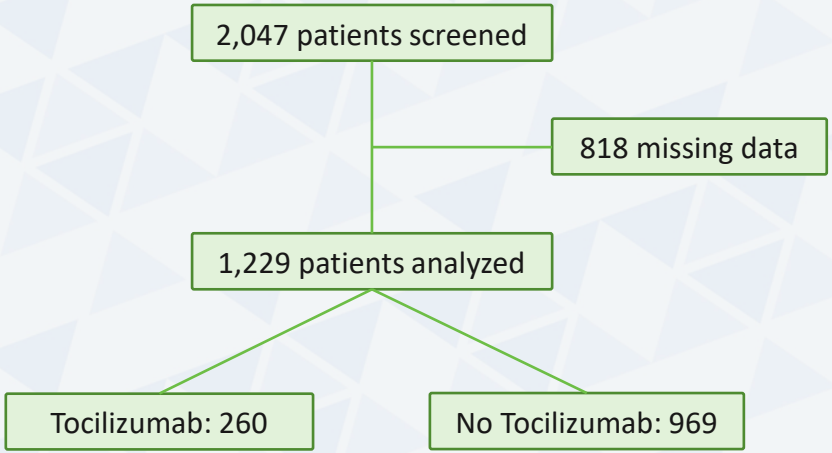
Tocilizumab (Actemra®) & Other IL-6 Antagonists

An Updated Review of Retrospective Studies

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Martinez-Sanz J, et. al.

Effect of Tocilizumab on Mortality in Hospitalized Patients with COVID-19: A Multicenter Cohort Study



Characteristic	Control group (n = 969)	Tocilizumab (n = 260)	P-value
Age, median (IQR)	68 (57 - 80)	65 (55 - 76)	0.017
Gender, n (%) - Male - Female	574 (59) 395 (41)	191 (73) 69 (27)	<0.001
Past medical history, n (%) - Hypertension - Diabetes	227 (23) 233 (24)	44 (17) 47 (18)	0.042
Vital signs at admission - Peripheral O_2 saturation (%), median (IQR)	94 (92-96)	91 (86-94)	<0.0001
Baseline laboratory - ALC (cells/µL), median (IQR) - LDH (U/L), median (IQR) - CRP (mg/L), median (IQR) - IL- 6 (pg/mL), median (IQR)	1050 (770 - 1440) 523 (408 - 664) 64 (27 - 122) 27 (7 - 60)	890 (630 - 1225) 669 (566 - 829) 113 (64 - 220) 70 (26 - 182)	<0.001 <0.001 <0.001 <0.001

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Martinez-Sanz J, Muriel A, Ron R, et al. *Clinical Microbiology and Infection* 2020. DOI: https://doi.org/10.1016/j.cmi.2020.09.021

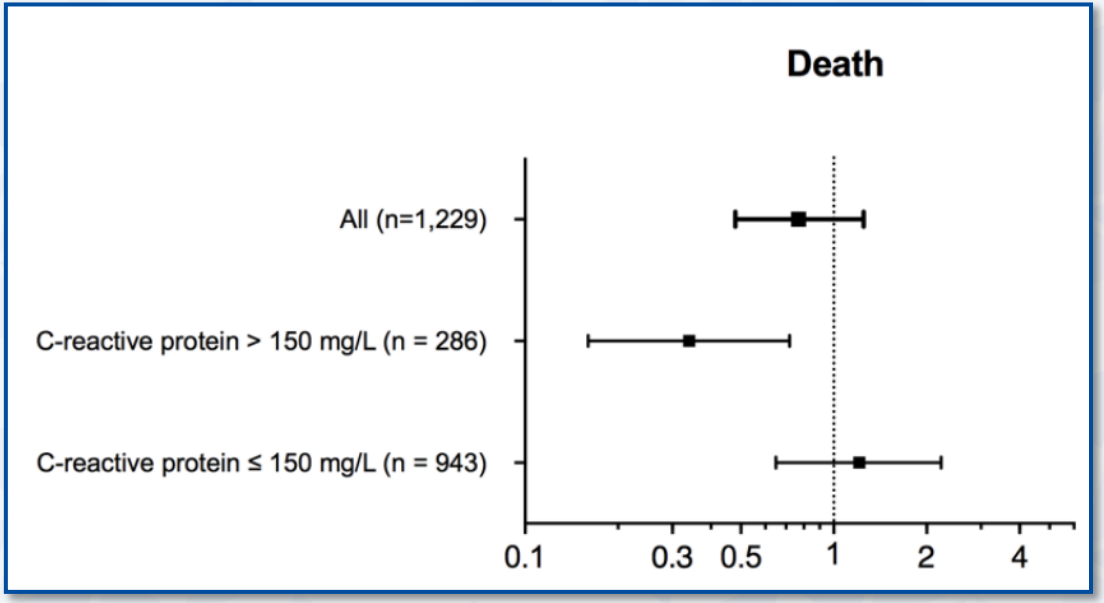
Results

Unadjusted Outcomes for the Overall Cohort			
Outcomes	**Control group (n=969)**	**Tocilizumab (n=260)**	**P-value**
Non-ICU length of stay (days), median (IQR)	8 (5-10)	13 (10-18)	<0.001
ICU admission, n (%)	32 (3)	50 (19)	<0.001
ICU length of stay (days), median (IQR)	2 (1-3)	6 (2-11)	0.002
Mortality, n (%)	120 (12)	61 (23)	<0.001
ICU or mortality, n (%)	120 (12)	66 (25)	<0.001

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Martinez-Sanz J, Muriel A, Ron R, et al. *Clinical Microbiology and Infection* 2020. DOI: https://doi.org/10.1016/j.cmi.2020.09.021

Primary Outcome



Time to death[1]
HR 1.53, 95% CI 1.20-1.96, p=0.001

1. Unadjusted analysis, overall cohort

Time to death, CRP < 150 mg/L[2]
aHR 1.21, 95% CI 0.65-2.23, p=0.552

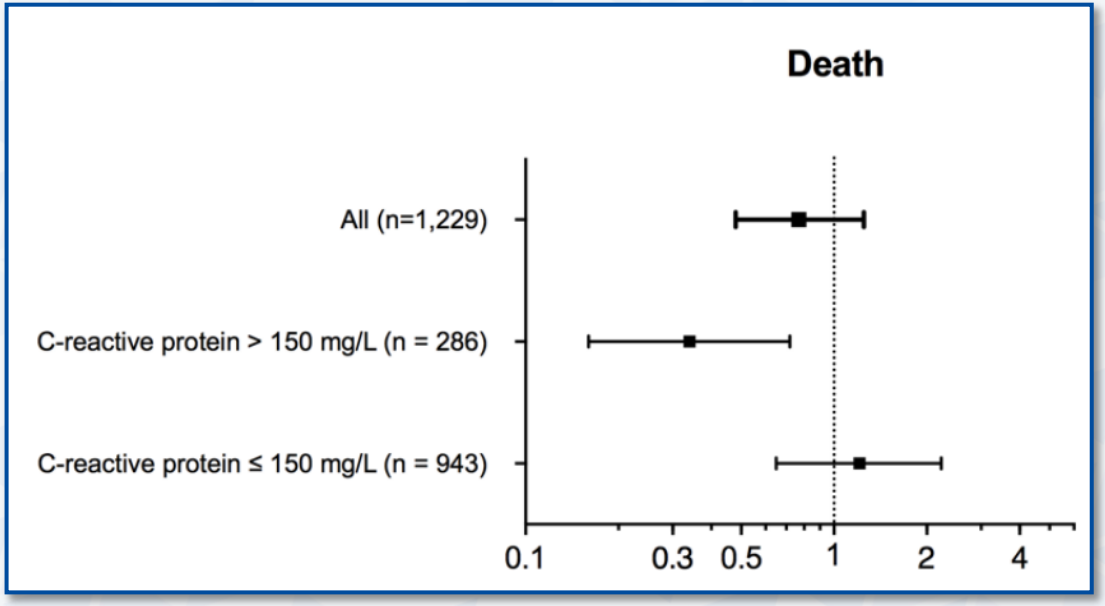
Time to death, CRP ≥ 150 mg/L[2]
aHR 0.34, 95% CI 0.17-0.71, p=0.005

2. Adjusted for sex, age, comorbidities, need for oxygen therapy at baseline, oxygen blood saturation, blood pressure, heart, rate, laboratory markers (time-varying parameters of severity)

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Martinez-Sanz J, Muriel A, Ron R, et al. *Clinical Microbiology and Infection* 2020. DOI: https://doi.org/10.1016/j.cmi.2020.09.021

Secondary Outcome



Time to ICU/death[1]
HR 1.77, 95% CI 1.41-2.22, p<0.001

1. Unadjusted analysis, overall cohort

Time to ICU/death, CRP < 150 mg/L[2]
aHR 1.41, 95% CI 0.77-2.58, p=0.264

Time to ICU/death, CRP ≥ 150 mg/L[2]
aHR 0.39, 95% CI 0.19-0.80, p=0.011

2. Adjusted for sex, age, comorbidities, need for oxygen therapy at baseline, oxygen blood saturation, blood pressure, heart, rate, laboratory markers (time-varying parameters of severity)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Martinez-Sanz J, Muriel A, Ron R, et al. *Clinical Microbiology and Infection* 2020. DOI: https://doi.org/10.1016/j.cmi.2020.09.021

Take Home Points

Strengths:

- Control group
- Controlled for indication bias using weighted marginal structural model and IPTW
- Signal that tocilizumab may be linked to improved outcomes in patients with systemic inflammation (elevated CRP)

Limitations:

- Retrospective, observational
- Selection bias introduced by missing data
- Standard of care not described
- No safety analysis

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

IPTW: inverse-probability treatment weight; CRP: C-reactive protein

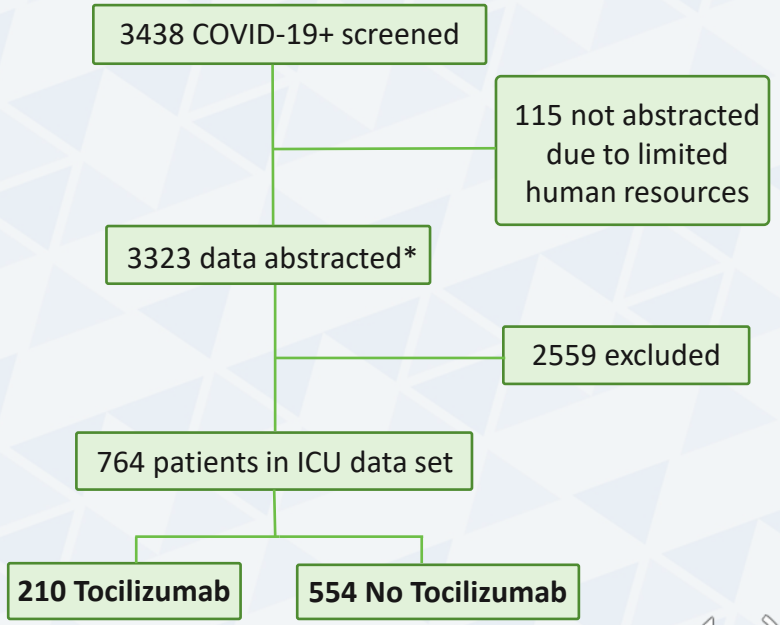
Martinez-Sanz J, Muriel A, Ron R, et al. 2020; pre-print, not peer-reviewed. https://doi.org/10.1101/2020.06.08.20125245

Biran N et. al.

Tocilizumab Among Patients with COVID-19 in the Intensive Care Unit: A Multicenter Observational Study

Baseline Characteristic*	Tocilizumab (n = 420)	No Tocilizumab (n = 210)	P-value
Nursing home resident, n (%)	11 (5%)	42 (10%)	0.047
Hospital setting, n (%) - Non-academic	178 (85%)	232 (55%)	<0.0001
Treatment, n (%) - Hydroxychloroquine - Azithromycin	199 (95%) 141 (67%)	355 (85%) 213 (51%)	<0.0001
Initial vital signs - FiO2%, median (IQR)	100 (100-100)	100 (85-100)	<0.0001
Initial laboratory tests - IL-6 (pg/mL), median (IQR) - D-dimer (µg/mL), mean	29 (9-96) 1.63	18.5 (7.0-49.75) 0.98	0.049 0.016

*Propensity score-matched cohort (n = 630)



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Biran N, Ip A, Ahn J, et al. *The Lancet Rheumatology* 2020. 2(10):E603-612. https://doi.org/10.1016/S2665-9913(20)30277-0

Tocilizumab Dosing

- 210 (98%) received 400 mg flat dose, two (1%) received 8 mg/kg, two (1%) received other doses
- Tocilizumab was administered a median of 9 days (IQR 6-12) after the start of symptoms
  - Median of 3 (1-7) days from hospitalization
  - Median of 0 (0-2) days from ICU admission
  - Median follow up for propensity-score matched cohort was 22 days (IQR 11-53)

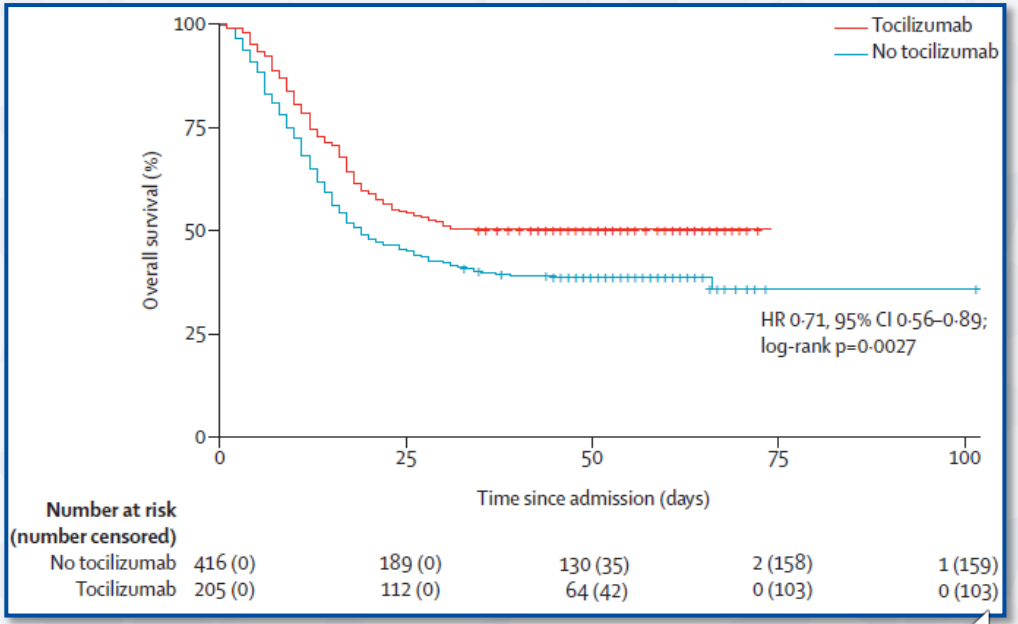
SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Biran N, Ip A, Ahn J, et al. *The Lancet Rheumatology* 2020. 2(10):E603-612. https://doi.org/10.1016/S2665-9913(20)30277-0

Results: Primary Outcome

Time to Hospital Mortality*
256 (61%) vs 102 (49%)
HR 0.71 (95% CI 0.56-0.89; p=0.0027)

*Data available for 621 patients in propensity-matched cohort; comparisons are no tocilizumab vs tocilizumab



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Biran N, Ip A, Ahn J, et al. *The Lancet Rheumatology* 2020. 2(10):E603-612. https://doi.org/10.1016/S2665-9913(20)30277-0

Variables Associated with Mortality

Propensity Score-matched Multivariable Cox Regression Model (n=616)		
Variable	**Estimated HR (95% CI)**	**P-value**
Tocilizumab, yes vs no	0.64 (0.47-0.87)	0.0040
Age, ≥ 65 vs < 65 years	2.00 (1.58-2.53)	<0.0001
Gender, female vs male	0.68 (0.53-0.86)	0.0015
Hypertension, yes vs no	1.44 (1.13-1.84)	0.0031
CRP > 15 mg/dL, missing vs no	2.11 (1.49-2.98)	<0.0001
Intubation, yes vs no	8.78 (2.79-27.61)	0.0002

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Biran N, Ip A, Ahn J, et al. *The Lancet Rheumatology* 2020. 2(10):E603-612. https://doi.org/10.1016/S2665-9913(20)30277-0

Subgroup Analysis

Multivariable Cox Regression Model by Age

Age < 65 (n=307)

Variable	Estimated HR (95% CI)	P-value
Tocilizumab, yes vs no	0.63 (0.44-0.94)	0.023
Gender, female vs male	0.57 (0.37-0.90)	0.015
Hypertension, yes vs no	1.54 (1.07-2.21)	0.02
Cancer, yes vs no	1.82 (1.02-3.22)	0.041
Renal failure, yes vs no	2.19 (1.12-4.25)	0.021
qSOFA score, 1 vs 0	1.73 (1.16-2.59)	0.0074

Age ≥ 65 (n=312)

Variable	Estimated HR (95% CI)	P-value
Tocilizumab, yes vs no	0.71 (0.48-1.04)	0.73
Gender, female vs male	0.74 (0.55-0.99)	0.042
Hypertension, yes vs no	1.39 (1.00-1.91)	0.047
Steroids, missing vs no	1.93 (1.15-3.24)	0.013
CRP ≥ 15 mg/dL, missing vs no	2.31 (1.46-3.65)	0.0003

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Biran N, Ip A, Ahn J, et al. *The Lancet Rheumatology* 2020. 2(10):E603-612. https://doi.org/10.1016/S2665-9913(20)30277-0

Subgroup Analysis

Multivariable Cox Regression Model by C-Reactive Protein (CRP) Level

CRP < 15 mg/dL (n=272)		
Variable	**Estimated HR (95% CI)**	**P-value**
Tocilizumab, yes vs no	0.92 (0.57-1.48)	0.73
Age, ≥ 65 vs < 65 years	1.83 (1.28-2.62)	0.001
Gender, female vs male	0.59 (0.41-0.85)	0.0041
Hypertension, yes vs no	1.89 (1.26-2.85)	0.0023
Intubation, yes vs no	9.14 (2.24-37.33)	0.0021

CRP ≥ 15 mg/dL (n=286)		
Tocilizumab, yes vs no	0.48 (0.30-0.77)	0.0025
Age, ≥ 65 vs < 65 years	1.97 (1.39-2.78)	0.0001
Oxygenation <94%, missing vs no	0.17 (0.04-0.81)	0.026
Intubation, yes vs no	8.56 (1.18-62.03)	0.034

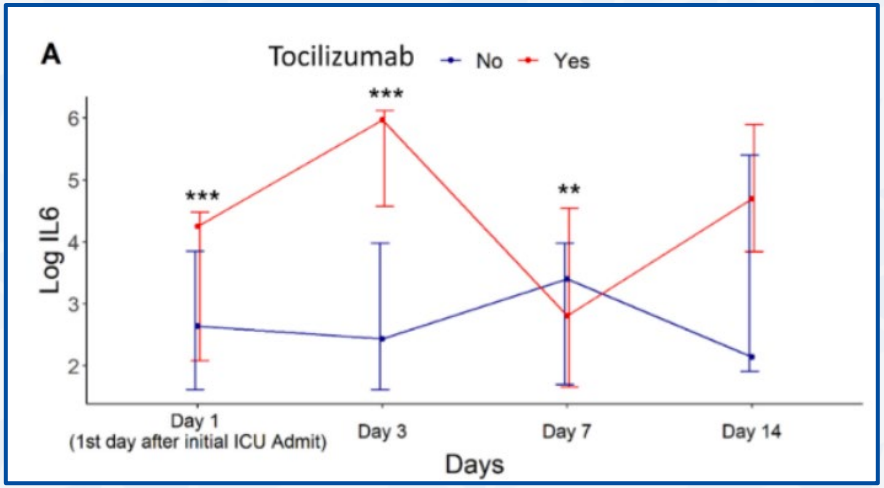
SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Biran N, Ip A, Ahn J, et al. *The Lancet Rheumatology* 2020. 2(10):E603-612. https://doi.org/10.1016/S2665-9913(20)30277-0

Secondary Outcomes

- Secondary bacterial infections: 17% in TCZ group vs 13% in SOC
- Vasopressor support was used equally regardless of TCZ use
- No association between reduction in FiO2 and receipt of TCZ at 1 day after treatment or TCZ and changes in SpO2 in blood

TCZ: tocilizumab; SOC: standard of care



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Biran N, Ip A, Ahn J, et al. *The Lancet Rheumatology* 2020. 2(10):E603-612. https://doi.org/10.1016/S2665-9913(20)30277-0

Take Home Points

Strengths:

- Control group
- Propensity-matched
- Cox-regression adjusted for possible confounders

Limitations:

- Retrospective (misclassification of data; inferences only, sampling bias)
- Missing data
- Indication bias – criteria for tocilizumab use not clear
- No IPTW adjustment
- Generalizability (NJ only)
- Adjusted for use of steroids but not other therapies

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

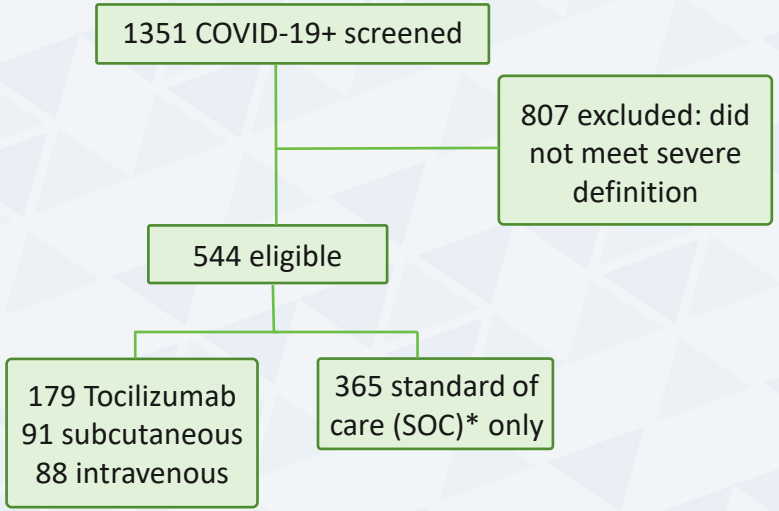
Biran N, Ip A, Ahn J, et al. *The Lancet Rheumatology* 2020. 2(10):E603-612. https://doi.org/10.1016/S2665-9913(20)30277-0

TESEO Study

Tocilizumab in Patients with Severe COVID-19: A Retrospective Cohort Study (TESEO)

Baseline Characteristic	SQ Toci (n=91)	IV Toci (n=88)	Overall (n=179)	SOC (n = 365)	P-value
Age (years)	67 (55-73)	63 (54-72)	64 (54-72)	69 (57-78)	0.0064
P/F (mmHg)	199 (123-262)	145 (102-229)	169 (106-246)	277 (191-345)	<0.0001
SOFA Score	2 (1-3)	3 (2-4)	3 (2-4)	2 (0-3)	0.0004
Days from sx onset	8 (5-10)	4 (3-8)	7 (4-10)	5 (2-9)	0.0017
Outcomes					
Follow-up (days)	12 (6-17)	13 (7-18)	12 (6-17)	8 (4-14)	<0.0001
Death	7 (8%)	6 (7%)	13 (7%)	73 (20%)	0.0007

SQ: subcutaneous; IV: intravenous; sx: symptom; SOFA: sequential organ failure assessment; Data presented as median (IQR) or n(%)



SOC: supplemental oxygen, hydroxychloroquine, azithromycin, lopinavir-ritonavir, darunavir-cobicistat, low molecular weight heparin prophylaxis, at physician's discretion

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. *The Lancet Rheumatology* 2020. 2(8):E474-484. https://doi.org/10.1016/S2665-9913(20)30173-9

Tocilizumab Dosing

- Due to national shortages, a random subset of patients eligible for tocilizumab did not receive the drug
- Intravenous tocilizumab: 8 mg/kg (maximum 800 mg), twice, 12h apart
- Subcutaneous tocilizumab: 162 mg in two simultaneous doses (each thigh)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. *The Lancet Rheumatology* 2020. 2(8):E474-484. https://doi.org/10.1016/S2665-9913(20)30173-9

Primary Outcome

Table 4: Unadjusted and adjusted relative hazards of the composite of the initiation of invasive mechanical ventilation or death

	Unadjusted analysis		Adjusted analysis*		Adjusted analysis†	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Overall (two-way contrast)						
Standard of care	1 (ref)	..	1 (ref)	..	1 (ref)	..
Tocilizumab (any)	0·60 (0·43–0·84)	0·0030	0·64 (0·45–0·91)	0·012	0·61 (0·40–0·92)	0·020
Tocilizumab (any)‡	0·54 (0·37–0·78)	0·0009	..	..	0·53 (0·31–0·89)§	0·016
Baseline PaO_2/FiO_2 ≤150 mm Hg (two-way contrast)						
Standard of care	1 (ref)	..	1 (ref)	..	1 (ref)	..
Tocilizumab (any)¶	0·30 (0·17–0·52)	..	0·20 (0·11–0·36)	..	0·19 (0·08–0·44)	..
Interaction p value ¶	..	..	..	..	..	0·011
Baseline PaO_2/FiO_2 >150 mmHg (two-way contrast)						
Standard of care	1 (ref)	..	1 (ref)	..	1 (ref)	..
Tocilizumab (any)¶	0·31 (0·16–0·59)	..	0·39 (0·20–0·77)	..	0·46 (0·21–0·99)	..
Overall comparison (three-way contrast)						
Standard of care	1 (ref)	..	1 (ref)	..	1 (ref)	..
Subcutaneous tocilizumab	0·63 (0·41–0·97)	0·036	0·69 (0·44–1·08)	0·102	0·65 (0·39–1·11)	0·11
Intravenous tocilizumab	0·57 (0·36–0·90)	0·016	0·60 (0·38–0·95)	0·030	0·55 (0·31–0·98)	0·042
Intravenous tocilizumab	1 (ref)	..	1 (ref)	..	1 (ref)	..
Subcutaneous tocilizumab	1·10 (0·61–1·95)	0·76	1·14 (0·63–2·05)	0·67	1·18 (0·59–2·36)	0·64
Standard of care	1·75 (1·11–2·75)	0·016	1·66 (1·05–2·62)	0·030	1·80 (1·02–3	0·042

*P/F ratio unavailable for 152 patients, excluded from stratified analysis
*Adjusted for age, sex, and recruiting centre.
†Adjusted for age, sex, recruiting centre, duration of symptoms, and SOFA score.
‡Using a weighted Cox instead of standard Cox model.
§Adjusted for age, sex, recruiting centre, duration of symptoms, SOFA score, use of steroids after baseline, and censoring using inverse probability weighting.

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. *The Lancet Rheumatology* 2020. 2(8):E474-484. https://doi.org/10.1016/S2665-9913(20)30173-9

Additional Outcomes

- Death: significant reduction in risk for tocilizumab treatment compared with SOC (aHR 0·38, 95% CI 0·17–0·83; p=0·015)
- AST elevations: no difference between groups
- 13% of the tocilizumab group were diagnosed with new infections, versus 4% in the SOC group (p<0·0001)

SOC: standard of care; AST: aspartate aminotransferase; *Adjusted for age, sex, and recruiting centre.

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. *The Lancet Rheumatology* 2020. 2(8):E474-484. https://doi.org/10.1016/S2665-9913(20)30173-9

Take Home Points

Strengths:

- Control group
- Cox-regression adjusted for possible confounders
- Inverse probability of treatment weighting used to account for non-randomization of treatment
- Assessed efficacy of subcutaneous tocilizumab
- Safety analysis

Limitations:

- Retrospective (misclassification of data; inferences only, sampling bias)
- Indication bias cannot be excluded (Tocilizumab use based on provider discretion)
- Generalizability (Italy only)
- Adjusted for use of steroids but not other therapies

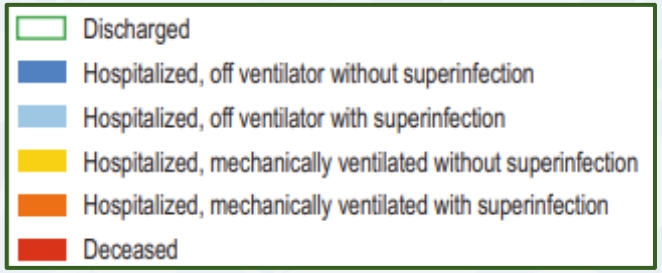
SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

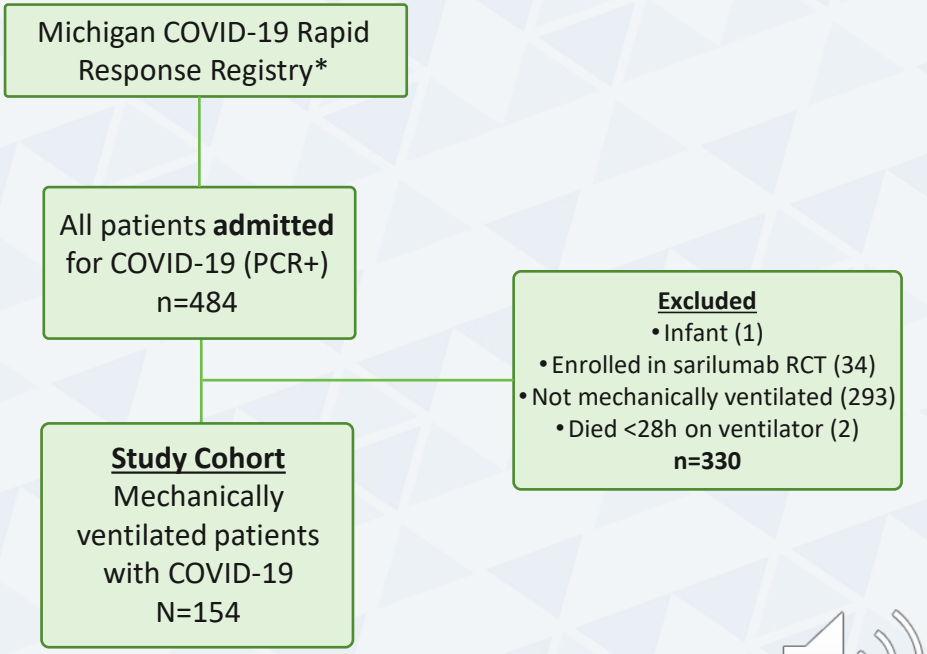
Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. *The Lancet Rheumatology* 2020. 2(8):E474-484. https://doi.org/10.1016/S2665-9913(20)30173-9

Somers et. al.

Tocilizumab for Treatment of Mechanically Ventilated Patients with COVID-19

- Primary outcome: Survival probability after intubation
- Secondary outcome: Clinical status at day 28 on a 6-level ordinal scale of illness severity





*All Michigan Medicine patients with confirmed or suspected COVID[illegible]ness o[illegible] positive SARS-CoV-2 test; PCR: polymerase-chain reaction

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954

Tocilizumab Usage Criteria

Michigan Medicine Guidance

- Abnormal chest imaging consistent with COVID-19
- Rapidly worsening gas exchange/respiratory status over 24-48 hours and requiring ≥4-6 L/min O_2
- Absence of systemic bacterial or fungal co-infection
- High clinical suspicion for CRS supported by elevated inflammatory markers and clinical decline
- Does not have a poor prognosis (unlikely to survive >48h)
- Mechanical ventilation for ≤48h

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954

Balancing After the Inverse Probability of Treatment Weighting (IPTW)

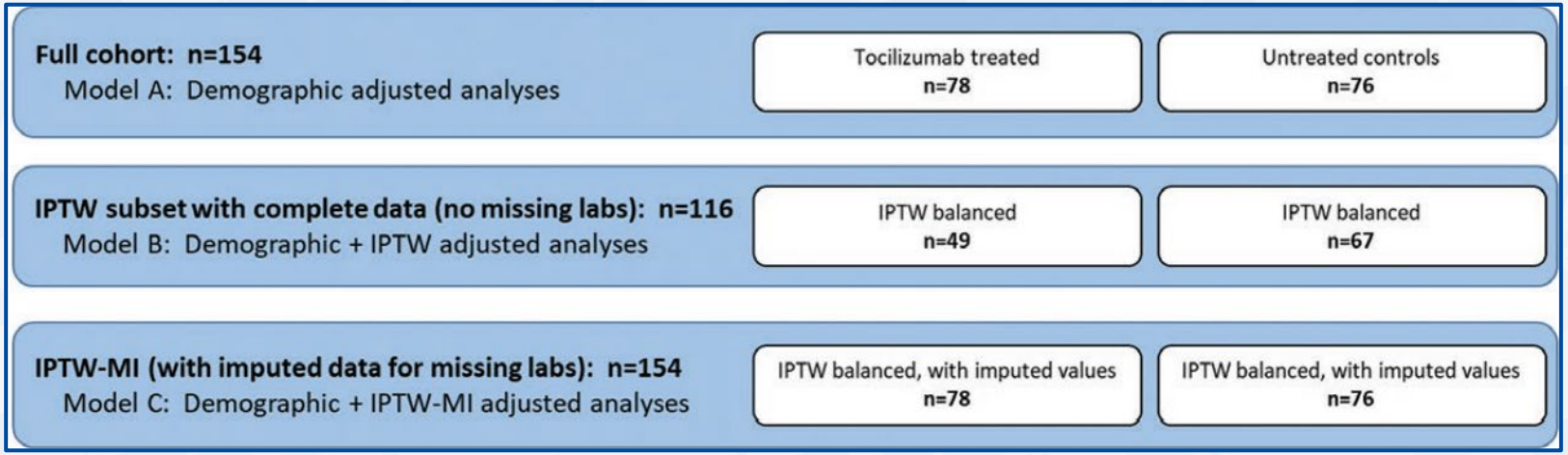
Characteristic	Pre-IPTW			Post-IPTW		
	tocilizumab-treated	tocilizumab-untreated	*p*-value	tocilizumab-treated	tocilizumab-untreated	*p*-value
Age, Mean (SD)	53 (16.0)	61 (14.2)	<0.001	57 (22.3)	57 (20.4)	0.78
Congestive heart failure, %	16	25	0.24	24	22	0.72
Chronic pulmonary disease, %	10	27	0.03	18	20	0.78
Chronic renal disease, %	35	49	0.12	44	44	0.93
Therapeutic anticoagulation, %	82	68	0.08	81	75	0.28
Ferritin, Mean (SD)	1854 (2525)	2199 (2513)	0.47	1969 (3512)	1998 (2991)	0.95
LDH, Mean (SD)	746 (403)	712 (569)	0.78	704 (531)	722 (646)	0.81
AST, Mean (SD)	101 (88)	183 (652)	0.38	98 (119)	145 (658)	0.49

(n=116)

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954

Study Models



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954

Baseline Characteristics

Baseline Characteristic	Overall (n=154)	TCZ (n=78)	No Toci (n=76)	P-value
Age (years), mean ± SD	58 ± 14.9	55 ± 14.9	60 ± 14.5	0.05
Outside Hospital Transfer, n(%)	101 (66)	45 (58)	56 (74)	0.04
Transfer on MV, n(%)	74 (48)	31 (40)	43 (57)	0.04
Chronic Pulmonary Disease, n(%)	29 (19)	8 (10)	21 (28)	0.006
Chronic Kidney Disease, n(%)	64 (42)	27 (35)	37 (49)	0.08

TCZ: Tocilizumab; MV: mechanical ventilation

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954

Treatment Characteristics

Other Notable Treatment Characteristics:

- No significant difference in concomitant medications received
- Tocilizumab was most often administered **within 24 hours of intubation**
  - 26% administered more than 48 hours after intubation.
  - Four patients in the tocilizumab group received a second dose
  - Patients who received tocilizumab were significantly more likely to be proned
- Timing to mechanical ventilation:
  - 45% of patients who were transferred were intubated >48h before transfer
  - 65% of patients intubated at Michigan Medicine were intubated within the first 24h of presentation

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

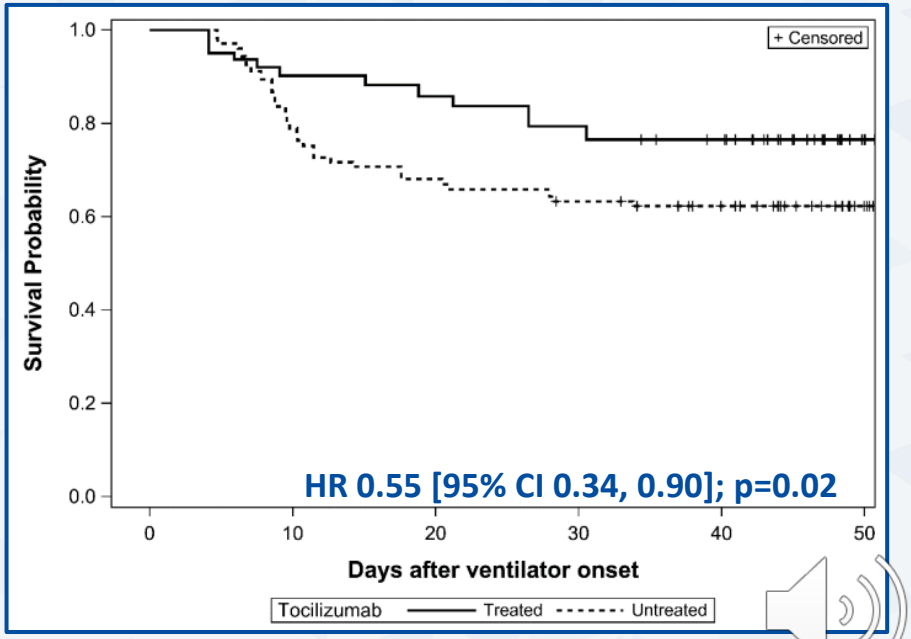
Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954

Primary Outcome

Tocilizumab for Treatment of Mechanically Ventilated Patients with COVID-19

- Median follow-up time was 47 days (range, 28–67 days)
- Survival probability was significantly higher among tocilizumab-treated compared with untreated patients:
  - Unadjusted analysis (p=0.0189)
  - IPTW-adjusted (complete laboratory data, right)
  - IPTW-MI adjusted (imputed laboratory data, full cohort) (HR, 0.54; 95% CI, 0.35–0.84); p=0.01
- Case fatality rate at 14, 21, and 28 days were also significantly lower for tocilizumab-treated patients (28 days: 18% vs 36%; p=0.01)

Inverse Probability of Treatment-Weighted Kaplan-Meier Curve of Survival (n=116)



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

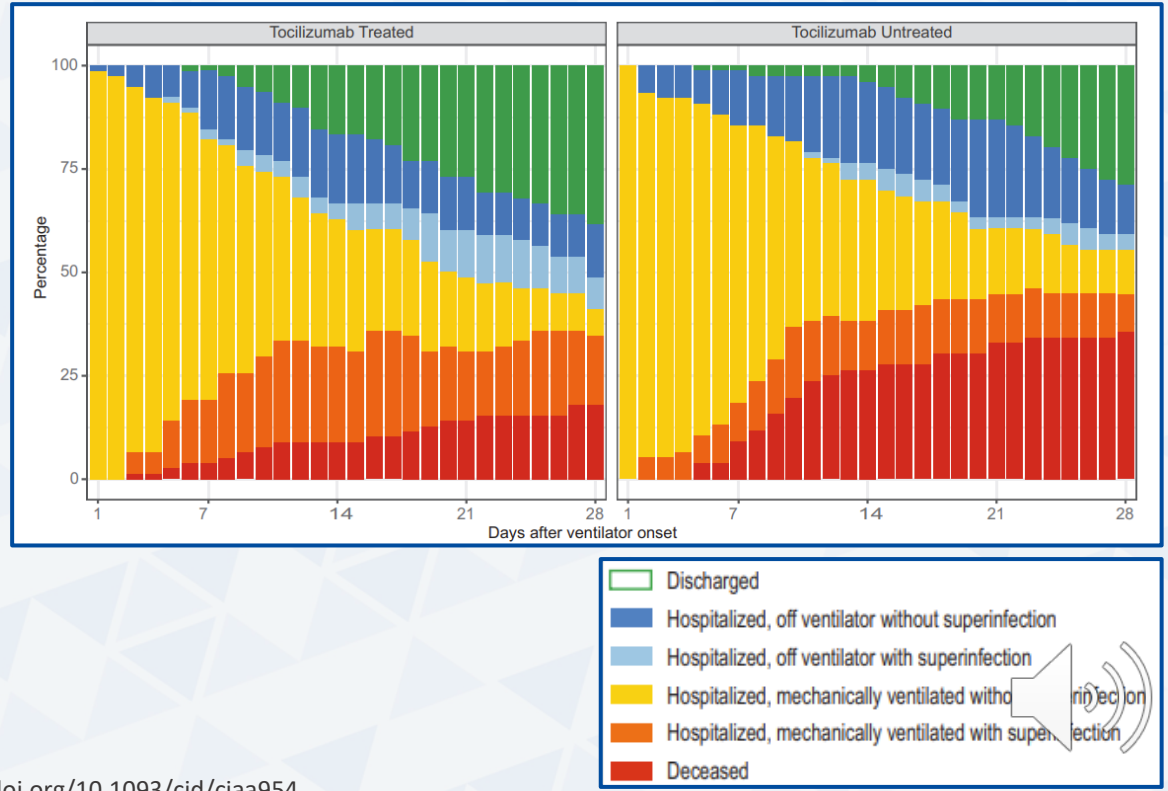
Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954

Secondary Outcome

- OR (95% CI)* estimates of the association between of tocilizumab and clinical status (ordinal outcome) at Day 28:
  - Model A: demographic adjusted 0.60 (0.34, 1.08) p=0.09
  - Model B: demographic + IPTW adjusted (n = 116) 0.58 (0.36, 0.94) p=0.03
  - Model C: demographic + IPTW-MI adjusted 0.60 (0.39, 0.91) p=0.02
- Tocilizumab was associated with improved status in all models

*Expressed as tocilizumab treated vs. untreated

Daily Distribution of Status on the 6-level Ordinal Scale Through Day 28



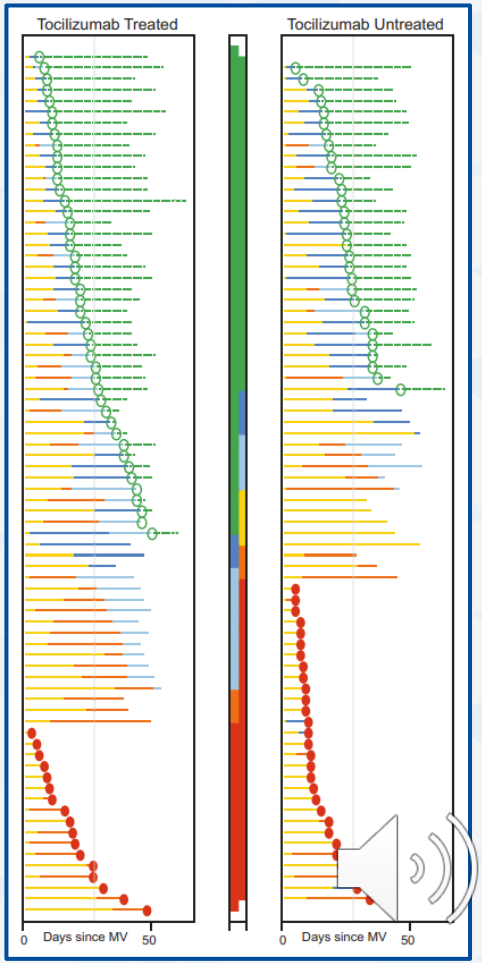
SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954

Individual Patient Trajectories

- Discharged alive: 56% vs 40%, p=0.04
- 17 patients in each group remaining hospitalized at the end of follow-up
  - Off mechanical ventilation: 82% vs 53%
- Patients who received tocilizumab were more than twice as likely to develop a superinfection than untreated controls (54% vs 26%; P < 0.001)
  - Driven primarily by VAP (45% vs 20%; P < .001)
- Among patients who received tocilizumab, there was no difference in 28-day case fatality rate for those with versus without superinfection (22% vs 15%; p=0.42)

*Expressed as tocilizumab treated vs. untreated; VAP: ventilator-associated pneumonia



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954

Take-Home Points

Tocilizumab for Treatment of Mechanically Ventilated Patients with COVID-19

Strengths:

- Control group, long follow-up period
- Accounted for non-random treatment allocation using inverse probability of treatment weighting
- Cox-regression adjusted for possible confounders
- Controlled for missing data using multiple imputation
- Results remained consistent across various sensitivity analyses

Limitations:

- Unknown course of disease from presentation to transfer (majority in the untreated group)
- Unknown significance of differences in medical management between groups (proning)
- Unknown hospitalization outcome for 34 patients (max follow up of 67 days)
- Signal of increased bacterial pneumonia in tocilizumab arm warrants RCTs

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954

Design: STOP-COVID

Association between Early Treatment with Tocilizumab and Mortality Among Critically ill Patients with COVID-19

- Inclusion:
  - Adults at least 18 years old
  - PCR confirmed SARS-CoV-2
  - ICU admission for COVID-19
- Exclusion:
  - Enrollment in clinical trial
  - Hospitalized > 1 week prior to ICU admission
  - AST or ALT > 500 U/L on ICU admission
  - Receipt of IL-6 antagonist other than TCZ
  - Receipt of TCZ prior to ICU admission

PCR: polymerase-chain reaction; ICU: intensive care unit; TCZ: tocilizumab

- Primary outcome: time to in-hospital death, censored at hospital discharge or last follow-up
- Secondary outcomes (unadjusted):
  - Secondary infection
  - Transaminitis
  - Arrhythmias
  - Thrombotic complications (within 14 days after ICU admission)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

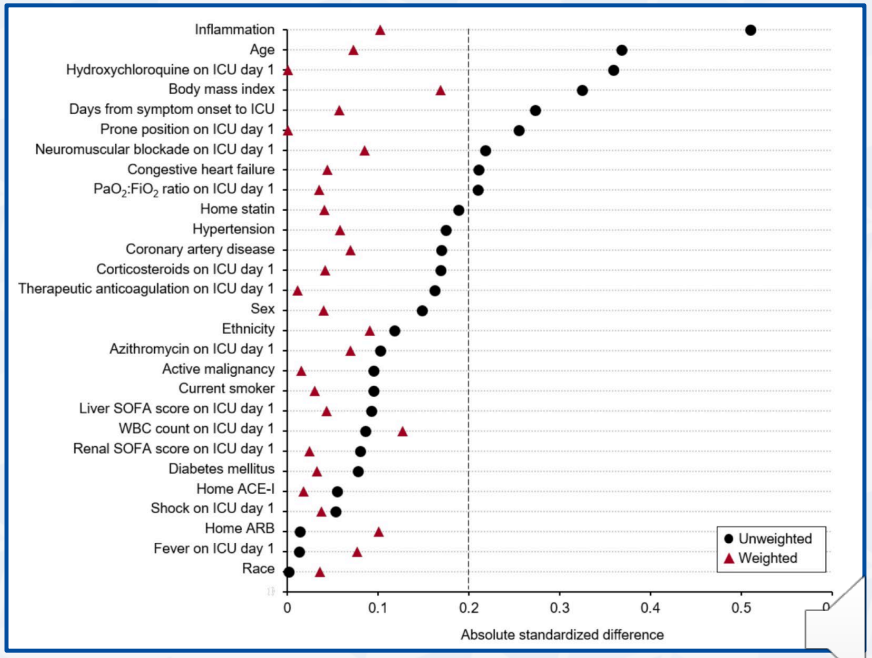
Gupta S, Wang W, Hayek SS, et al. *JAMA Intern Med*. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6252

Statistical Plan

- 28 baseline covariates
- Vertical dashed line: Standardized difference of 0.2
- Effects sizes below 0.2 considered to be small
- Baseline characteristics were well balanced after applying IPTW
- Missing data was not imputed*

IPTW: inverse probability of treatment weighting
*except renal and liver components of SOFA score

Standardized Differences Before and After Applying Inverse Probability Weighting

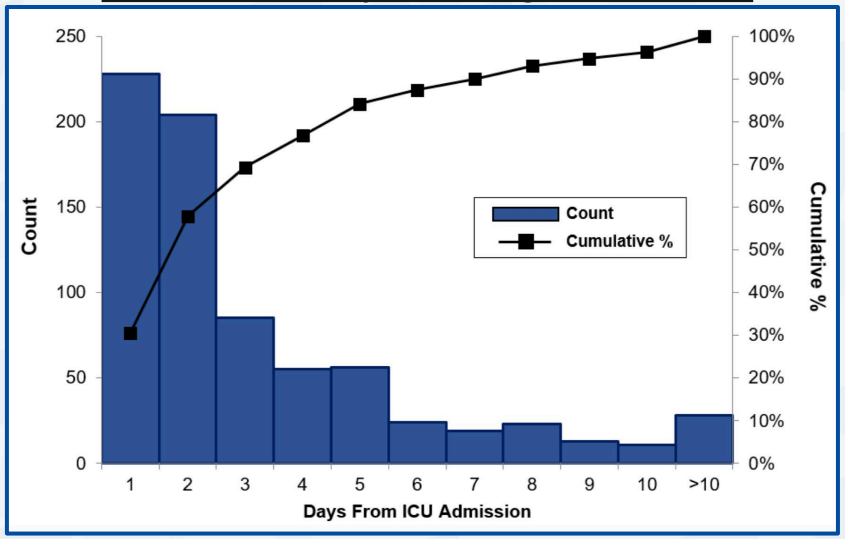


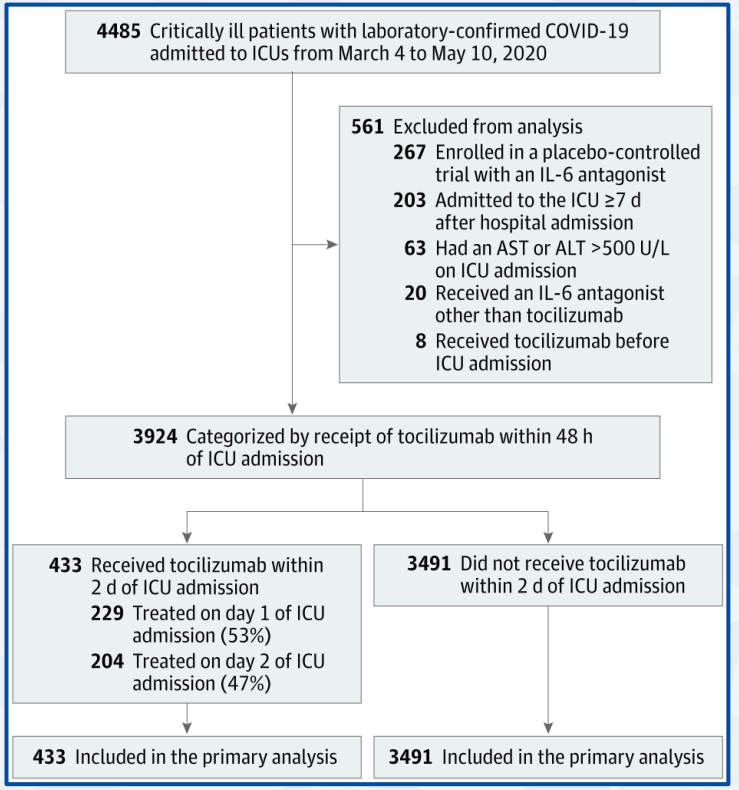
SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Gupta S, Wang W, Hayek SS, et al. *JAMA Intern Med*. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6252

Results

Distribution of Tocilizumab Receipt According to the Number of Days Following ICU Admission





SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Gupta S, Wang W, Hayek SS, et al. *JAMA Intern Med*. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6252

Baseline Characteristics

- Median age: 62 (IQR 52-71) years
- 62.8% male
- Before IPTW TCZ-treated patients:
  - Younger, median age (years): **58** [IQR, 48-65] vs **63** [IQR, 52-72]
  - Had fewer comorbidities:
    - Hypertension: 54.0% vs 62.6%
    - Coronary artery disease: 9.0% vs 14.4%
    - Congestive heart failure: 5.3% vs 11.1%
  - More likely to:
    - Have severe hypoxemia*: 47.3% vs 37.9%
    - Have elevated inflammatory markers (CRP, IL-6, ferritin): 85.7% vs 65.6%
    - Receive corticosteroids: 18.7% vs 12.6%

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

*Mechanical ventilation and a Pao2:Fio2 ratio <200 mm Hg; IQR: interquartile range; IPTW: inverse probability of treatment weighting; TCZ: tocilizumab; CRP: C-reactive protein; IL-6: interleukin 6

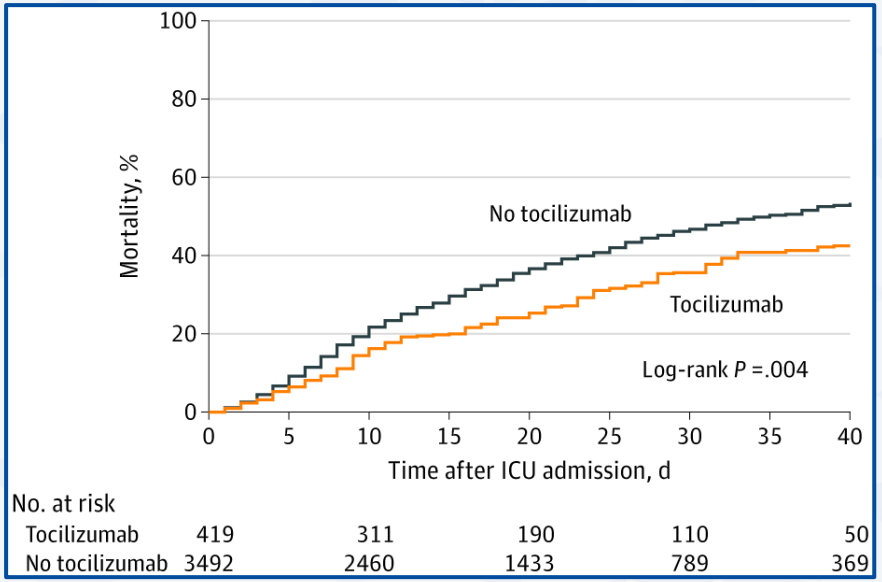
Gupta S, Wang W, Hayek SS, et al. *JAMA Intern Med*. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6252

Results

- In-hospital mortality:
  - Total cohort: n=1544 (39.3%)
  - 28.9% vs 40.6%* (unadjusted HR, 0.64; 95% CI, 0.54-0.77)
  - **TCZ-treated patients had a lower adjusted risk of death (HR, 0.71; 95% CI, 0.56-0.92)**
  - 30-day mortality*: 27.5% vs 37.1% (risk difference, 9.6%; 95% CI, 3.1%-16.0%)

*TCZ-treated vs TCZ-untreated

Mortality in Tocilizumab-Treated vs Non-Tocilizumab-Treated Patients



A total of 63 TCZ-treated and 259 non-TCZ–treated patients were still hospitalized at last follow-up and could not be fully [illegible]ssed for the primary outcome. ICU: indicates intensive care uni[illegible]

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

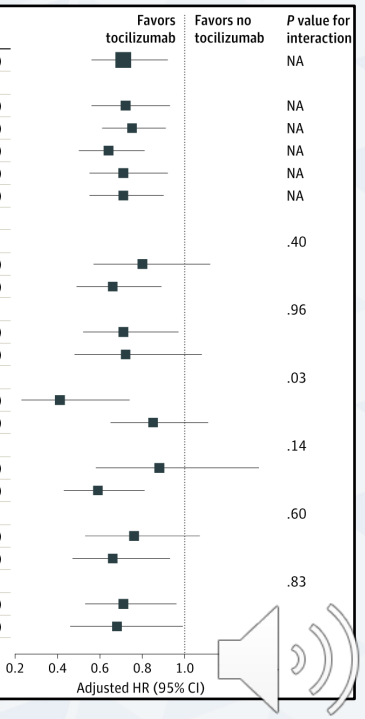
Gupta S, Wang W, Hayek SS, et al. *JAMA Intern Med*. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6252

Results

- Results remained similar across all 5 pre-specified sensitivity analyses:
  - With discharged patients kept in the risk set until last follow-up date
  - In the unweighted Cox regression model
  - In the nested target trial approach
  - In the analysis that excluded moribund patients
  - In the analysis that was adjusted for the number of pre-COVID ICU beds
- Association between tocilizumab and death was larger among patients admitted to the ICU within 3 days of symptom onset

Subgroup Analyses Examining Mortality in Tocilizumab-Treated vs Non-Tocilizumab–Treated Patients

Source	No. of deaths / No. of patients (%)		Adjusted HR (95% CI)	*P* value for interaction
	Tocilizumab	No tocilizumab		
Primary analysis	125/433 (28.9)	1419/3491 (40.6)	0.71 (0.56-0.92)	NA
Sensitivity analyses				
Without censoring at discharge	125/433 (28.9)	1419/3491 (40.6)	0.72 (0.56-0.93)	NA
Unweighted Cox model	125/433 (28.9)	1419/3491 (40.6)	0.75 (0.62-0.91)	NA
Nested target trial approach	125/433 (28.9)	1419/3491 (40.6)	0.64 (0.50-0.81)	NA
Exclusion of moribund patients[a]	119/426 (27.9)	1339/3392 (39.5)	0.71 (0.55-0.92)	NA
Adjustment for No. of ICU beds	125/433 (28.9)	1419/3491 (40.6)	0.71 (0.55-0.90)	NA
Subgroups				
Age, y				.40
<60	57/240 (23.8)	366/1425 (25.7)	0.80 (0.57-1.12)	
≥60	68/193 (35.2)	1053/2066 (51.0)	0.66 (0.49-0.89)	
Sex				.96
Male	88/299 (29.4)	925/2165 (42.7)	0.71 (0.52-0.97)	
Female	37/134 (27.6)	494/1326 (37.3)	0.72 (0.48-1.08)	
Time from symptom onset to ICU admission, d				.03
≤3	15/58 (25.9)	429/835 (51.4)	0.41 (0.23-0.74)	
>3	110/375 (29.3)	990/2656 (37.3)	0.85 (0.65-1.11)	
PaO_2:FiO_2 ratio on ICU admission				.14
≥200 Or not mechanically ventilated	48/188 (25.5)	581/1834 (31.7)	0.88 (0.58-1.35)	
<200 And mechanically ventilated	65/205 (31.7)	663/1322 (50.2)	0.59 (0.43-0.81)	
Vasopressor treatment on ICU admission				.60
No	68/254 (26.8)	769/2126 (36.2)	0.76 (0.53-1.07)	
Yes	57/179 (31.8)	650/1365 (47.6)	0.66 (0.47-0.93)	
Corticosteroid treatment on ICU admission				.83
No	91/352 (25.9)	1189/3051 (39.0)	0.71 (0.53-0.96)	
Yes	34/81 (42.0)	230/440 (52.3)	0.68 (0.46-0.99)	



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Gupta S, Wang W, Hayek SS, et al. *JAMA Intern Med*. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6252

Take-Home Points

Strengths:

- Large sample size; multiple sites (68), ICU-focus
- IPTW-adjusted for multiple comorbidities and severities of illness
- Several prespecified sensitivity analyses with consistent results

Limitations:

- Patients who received tocilizumab after the first 2 days of ICU admission were categorized in the non-tocilizumab–treated group (residual confounding)
- Relatively short follow-up period (median 27 days)
- Heterogeneity of usage criteria across sites (clinical differences among ICU patients)
- Missing data (inflammatory markers, Pao2:Fio2 ratios)
- No safety analysis

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Gupta S, Wang W, Hayek SS, et al. *JAMA Intern Med*. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6252

Summary: Retrospective Studies

Study	Population	Primary Outcome	Safety	Main Conclusion
Martinez-Sanz, et. al. 2020	Moderate disease, non-ICU	Time to death	No analysis	+ TCZ linked to decreased time to mortality in patients with systemic inflammation (elevated CRP)
Biran, et. al. 2020	Severe, ICU	Time to hospital mortality	No significant difference between groups in infection rates	+ TCZ associated with a reduction in hospital-related mortality in those <65 and in those with elevated CRP
Guaraldi et. al. 2020 (TESEO)	Severe, only 17% intubated	Composite of death or invasive mechanical ventilation	Significantly increased risk of secondary infections in the TCZ group	+ Significant reduction in risk of mechanical ventilation or death
Somers et. al. 2020 (Michigan Medicine)	Severe, intubated	Survival probability after intubation	Significantly increased risk of secondary infections in TCZ group	+ Survival probability was significantly higher among TCZ-treated patients
Gupta et. al. 2020 (STOP-COVID)	Severe, ICU	Time to mortality	No analysis	+ TCZ-treated patients had a lower adjusted risk of death

TCZ: tocilizumab; CRP: C-reactive protein

Tocilizumab (Actemra®) & Other IL-6 Antagonists

An Updated Review of Randomized Controlled Trials

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

RCT

RCT-TCZ-COVID-19

Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia

- Inclusion:
  - Adults at least 18 years old
  - PCR confirmed SARS-CoV-2
  - PaO_2/FiO_2 ratio 200-300 mmHg
  - Fever (>38 °C) during 2 days prior to randomization and/or serum CRP levels of ≥ 10 mg/dL and/or CRP doubled since admission
- Exclusion:
  - Invasive or non-invasive mechanical ventilation*
  - ICU admission
  - Tocilizumab hypersensitivity
  - Any condition preventing future admission to ICU

PCR: polymerase chain reaction; CRP: C-reactive protein
*After randomization, patients could receive non-invasive mechanical ventilation

- Primary outcome: composite of entry into the ICU with mechanical ventilation, death from all causes, or clinical aggravation (PaO_2/FiO_2 < 150 mm Hg), whichever came first.
- Secondary outcome: rate of patients admitted to the ICU with invasive mechanical ventilation at 14 and 30 days.

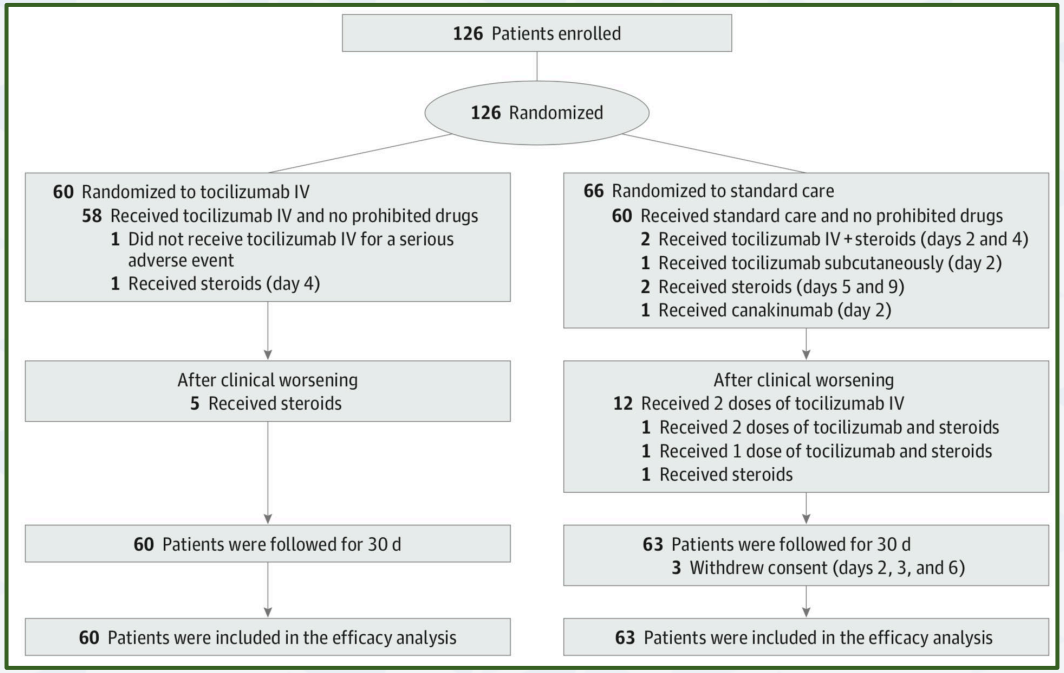
ICU: intensive care unit

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Salvarini C , Dolci G, Massari M, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615

RCT

Study Flowchart



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Salvarini C , Dolci G, Massari M, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615

RCT

Baseline Characteristics

Baseline Characteristic	Overall (n=126)	TCZ (n=60)	SOC (n=66)
Age (years), median (IQR)	60 (53-72)	61.5 (51.5-73.5)	60 (54-69)
Sex (male), n(%)	77 (61.1)	40 (66.7)	37 (56.1)
Obesity (BMI ≥ 30)	38 (32.2)	16 (28.1)	22 (36.1)
CRP, median (IQR), mg/dL	8.2 (3.7-13.5)	10.5 (5.0-14.6)	6.5 (3.2-11.8)
IL-6, median (IQR), pg/dL	42.1 (20.6-74.9)	50.4 (28.3-93.2)	34.3 (19.0-59.3)
Hydroxychloroquine, n(%)	115 (91.3)	53 (88.3)	62 (93.9)
Antiretrovirals, n(%)*	52 (41.3)	21 (35.0)	31 (47.0)
Azithromycin, n(%)	26 (20.6)	10 (16.7)	16 (24.2)

TCZ: tocilizumab; SOC: standard of care; IQR: interquartile range; BMI: body mass index; CRP: C-reactive protein; IL-6: interleukin 6
* darunavir/cobicistat, darunavir/ritonavir, or lopinavir/ritonavir

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

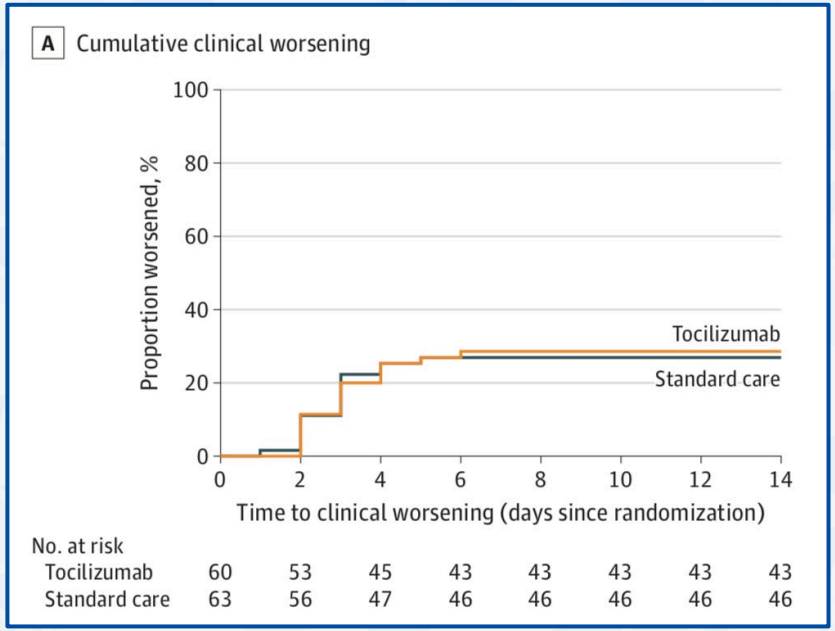
Salvarini C , Dolci G, Massari M, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615

Outcomes: ITT Population

- ICU admission within 14 days: n=14
  - 10.0% vs 7.9% (RR, 1.26; 95% CI, 0.41-3.91)
- Mortality at 14 days:
  - 1.7% vs 1.6% (RR, 1.05; 95% CI, 0.07-16.4)
- Clinical worsening:
  - 28.3% vs 27.0% (RR, 1.05; 95% CI, 0.59-1.86; p=0.87)
  - No difference in time to event

All comparisons are tocilizumab vs standard of care, within 14 days of randomization

Kaplan-Meier Estimates of Cumulative Clinical Worsening



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Salvarini C , Dolci G, Massari M, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615; ITT: intention-to-treat

RCT

Take-Home Points

Strengths:

- Randomized controlled trial, multiple sites (24)

Limitations:

- Prematurely interrupted after an interim analysis for futility (did not meet power); small sample size
- Open-label, not placebo-controlled (bias primary outcome assessment)
- Low overall mortality rate (external validity)
- Exclusion criteria introduced sampling bias
- Composite endpoint with components of varying clinical significance
- **Patients in the control arm allowed to receive tocilizumab as rescue therapy (23.3%)**

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Salvarini C , Dolci G, Massari M, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615

RCT

CORIMUNO-19-TOCI-1

Effect of Tocilizumab vs Usual Care in Adults Hospitalized with COVID-19 and Moderate or Severe Pneumonia

- Primary outcome:
  - Scores higher than 5 on the WHO-CPS on day 4
  - Survival without need of any ventilation on day 14
- Secondary outcomes:
  - WHO-CPS scores at day 7 and day 14
  - Overall survival
  - Time to discharge
  - Time to oxygen supply independency
  - Biological factors (i.e. CRP)
  - Adverse events

WHO-CPS: World Health Organization 10-point Clinical Progression Scale; CRP: C-reactive protein

WHO Clinical Progression Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820
WHO Working Group on the Clinical Characterization and Management of COVID-19 infection. *Lancet Infect Dis* 2020; 20: e192–97. doi: 10.1016/ S1473-3099(20)30483-7

RCT

Population

- Inclusion:
  - Adults at least 18 years old
  - PCR confirmed SARS-CoV-2 and/or typical CT chest findings
  - Moderate or severe pneumonia: WHO-CPS score of 5 receiving at least 3L/min oxygen but without HFO, NIV, or MV
- Exclusion:
  - Hypersensitivity to TCZ
  - Pregnancy
  - Documented bacterial infection
  - Patients with any of following laboratory results:
    - ANC < 1.0×10^9/L or less
    - Platelets < 50 g/L.

PCR: polymerase chain reaction; CT: computed tomography; HFO: high-flow oxygen; NIV: non-invasive ventilation; MV: mechanical ventilation; TCZ: tocilizumab; ANC: absolute neutrophil count

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

Statistical Plan

- Bayesian modeling for the co-primary outcomes
- Treatment effect expressed in terms of absolute risk difference (ARD) for the day 4 outcome and hazard ratio (HR) for the day 14 outcome.
- Posterior probabilities of ARD < 0 and HR < 1 were computed, representing the posterior probability of efficacy
- If these probabilities were > 0.95 at the final analysis, the treatment could be considered as showing efficacy
- Secondary outcomes not corrected for multiplicity

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

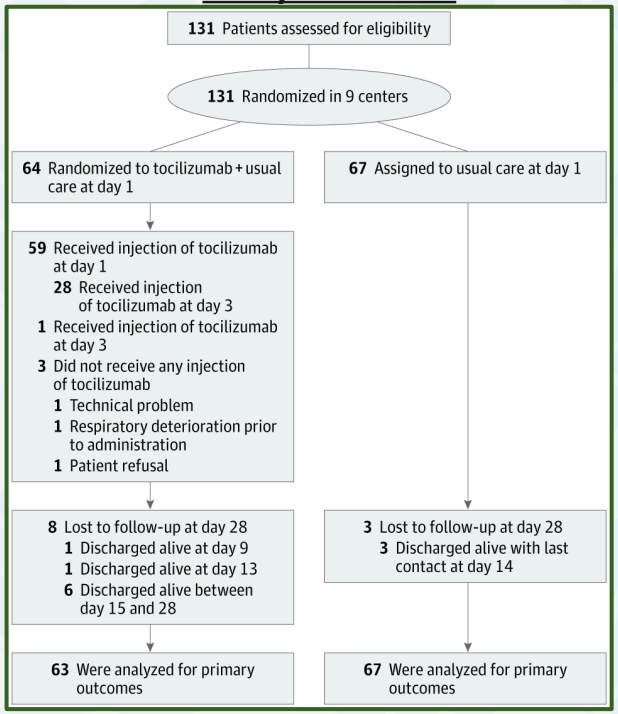
RCT

Results

Baseline Characteristics:

- No significant between-group differences at enrollment
- Median age: 64 years (IQR, 57.1-74.3); 88 (68%) men
- Median BMI ~27
- PCR-confirmed infection in 89% (TCZ) and 90% (SOC)
- Oxygen need at baseline: median 5L/min with median SpO2 of 95%
- Most common comorbidities: diabetes; chronic cardiac disease
- Concomitant medications, TCZ vs SOC:
  - Antiviral drugs (lopinavir/ritonavir): 7(11%) vs 16 (24%)
  - Glucocorticoids: 21 (33%) vs 41 (61%)
  - Immunomodulators: 1 (anakinra) vs 4 (anakinra, n = 3; eculizumab, n = 1)

Study Flowchart



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

Primary Outcome

eTable 3. Day 4 outcome.

In the protocol the D4 primary outcome is defined as a WHO-CPS score ≤ 5 at day 4, and patients with a new DNR at, or before, day 4 where considered as with a WHO-CPS score > 5. Results are presented as proportions with a WHO-CPS score > 5, so that an effective treatment would result in a risk reduction.

	Tocilizumab	UC	Absolute Risk Difference	Adjusted Odds Ratio
N	63	67		
N (%) WHO-CPS > 5	12 (19%)	19 (28%)		
Posterior Median	19.7%	28.8%	-9.0%	0.57
90% CrI			-21.0 to +3.1	0.28 to 1.15
95% CrI	11.3 to 30.5	19.0 to 40.1	-23.3 to +5.5	0.24 to 1.32
Posterior probabilities*				
P(Any benefit)			0.890	0.905
P(Moderate or greater benefit)			0.684	0.823

* P(Any benefit)=P(ARD < 0) or P(OR < 1), P(Moderate or greater benefit) = P(ARD < -5.5%) or P(OR < 0.85)

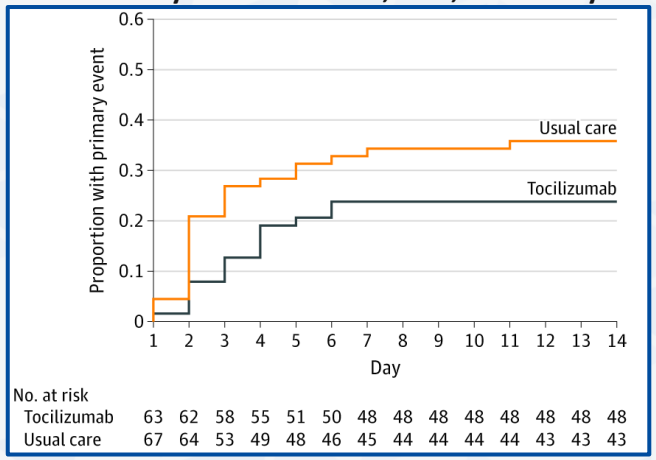
SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

Primary Outcome

Probability of death or MV, HFO, NIV at Day 14



HFO: high-flow oxygen; MV: mechanical ventilation; NIV: noninvasive ventilation.

Variable	Tocilizumab (n = 63)	UC (n = 67)	Difference (95% CI)
Primary outcome by day 14, No.	15	24	
Cumulative incidence, % (95% CI)	24 (13 to 34)	36 (23 to 46)	−12 (−28 to 4)
First event, No.			
NIV/HFO	8	13	
MV	3	8	
Death/DNR order	4	3	

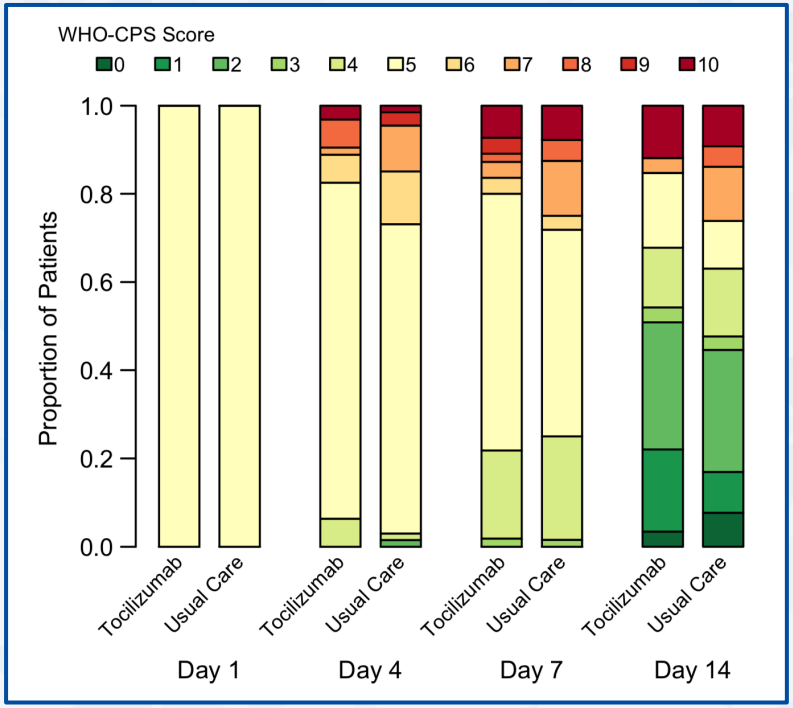
SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

Secondary Outcome

WHO Clinical Progression Scale Score During Follow-up



Numerically lower scores by day 14 for TCZ group, median (IQR):

- 2 (2 to 5) vs 4 (2 to 7) (adjOR*, 0.76; 95% CrI (0.40 to 1.42)

*odd ratio adjusted for age and center; TCZ: tocilizumab; IQR: interquartile range;

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

Secondary Outcomes

Outcome, Day 28	TCZ	SOC	aHR*	95% CI
Overall survival	7 deaths	8 deaths	0.92	0.33-2.53
Time to discharge, cumulative incidence, %(95% CI)	83 (70%-90%)	73 (61%-82%)	1.52	1.02-2.27
Time to oxygen supply independency, cumulative incidence, %(95% CI)	89 (78%-95%)	75 (62%-83%)	1.41	0.98-2.01

*hazard ratio adjusted for age and center; TCZ: Tocilizumab; SOC: standard of care; CI: confidence interval

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

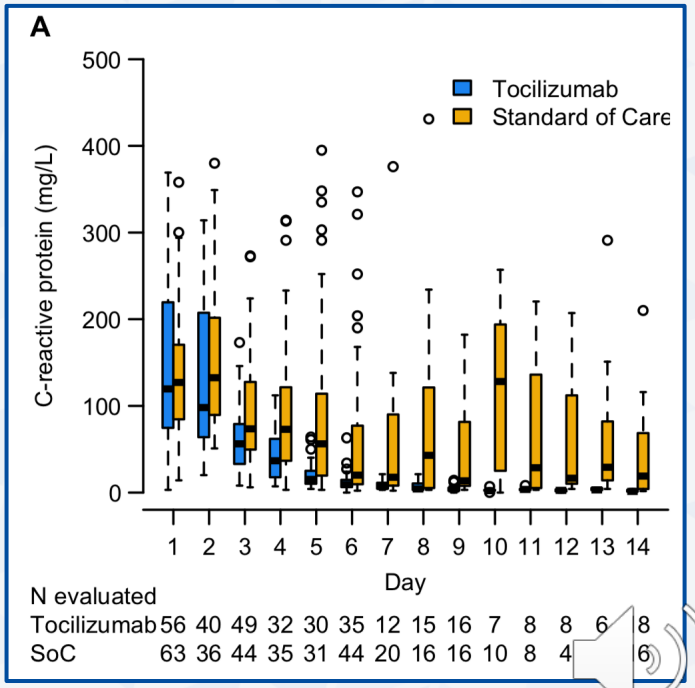
Secondary Outcomes

Adverse events (ADE)

- Most common: ARDS and bacterial sepsis
- Serious ADE, TCZ vs SOC: 20 (32%) vs 29 (43%); p=0.21
- Total number of serious ADE, TCZ vs SOC: 27 vs 57, p=0.003
  - Serious bacterial infections, TCZ vs SOC: 2 vs 11

TCZ: Tocilizumab; SOC: standard of care

Evolution of CRP



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

Take-Home Points

Strengths:

- Randomized controlled trial, multiple sites (9)
- Bayesian modeling of primary outcome
- Suggests that tocilizumab may improve clinical progression at 14 days; no effect on mortality

Limitations:

- Small sample size, open-label
- Short follow-up period
- Not all patients had PCR-confirmed disease (subgroup analyses completed)
- More patients in the SOC arm received glucocorticoids, despite randomization
- OR and HR adjusted only for age and center for primary/secondary outcomes
- Missing data considered primary outcome failure
- Do not resuscitate orders considered events

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

BACC Bay Tocilizumab Trial

Efficacy of Tocilizumab in Patients Hospitalized with COVID-19

- Intervention: randomly assigned (2:1) to tocilizumab (8 mg/kg) or placebo
- Primary outcome:
  - Time to intubation or death
- Secondary outcomes:
  - Time to clinical worsening*
  - Time to discontinuation of supplemental oxygen

PCR: polymerase-chain reaction; IgM: immunoglobulin M; CRP: C-reactive protein; LDH: lactate dehydrogenase
*Defined as an increase by at least 1-2 points on a 7-point scale from discharge/ready for discharge (=1) to death (=7)

- Inclusion:
  - Adults 19-85 years old
  - PCR or serum IgM antibody + SARS-CoV-2
  - At least one:
    - CRP > 50 m/L, ferritin > 500 ng/mL, a d-dimer > 1000 ng/mL, or LDH > 250 U/L
  - At least two of the following signs:
    - fever (>38°C) within 72h of enrollment
    - Pulmonary infiltrates
    - Need for supplemental oxygen (for SpO2 >92%)
- Exclusion:
  - Supplemental oxygen > 10L/min
  - Recent treatment with biologic agent
  - Diverticulitis

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. *NEJM*; Published online October 21, 2020. doi: 10.1056/NEJMoa2028836

RCT

Design

Clinical Improvement Scale	
1	Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or <= 2L supplemental oxygen)
2	Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen
3	Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen
4	ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5	ICU, requiring intubation and mechanical ventilation
6	ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy)
7	Death

Clinical worsening: increase by at least 1 point among patients who had been receiving supplemental oxygen at baseline or at least 2 points among those who had not been receiving supplemental oxygen at baseline

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. *NEJM*; Published online October 21, 2020. doi: 10.1056/NEJMoa2028836

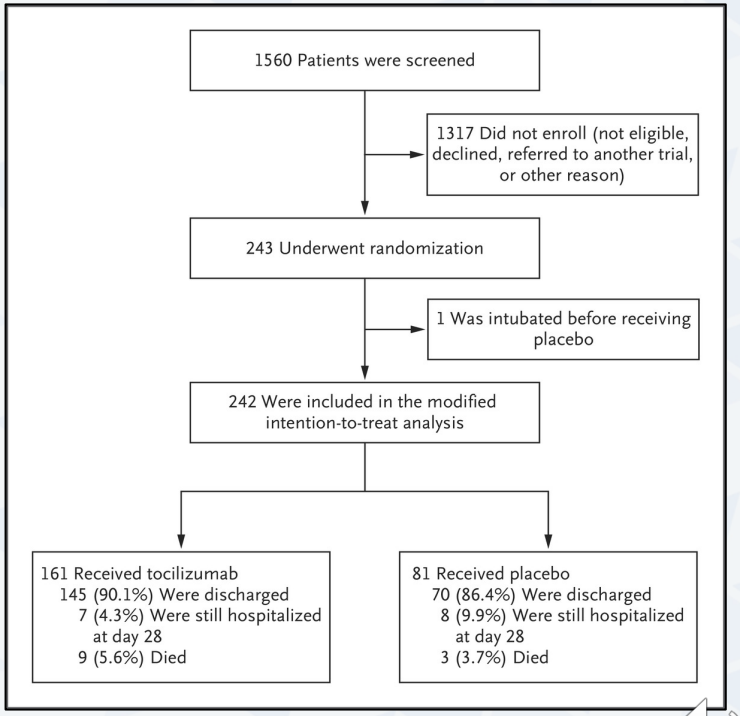
RCT

Results

Baseline Characteristics:

- Median age (years): 59.8 (IQR 45.3-69.4)
- 58.0% male; 45% Hispanic/Latino
- 80% hospitalized in non-ICU hospital wards and receiving supplemental oxygen (≤6 L/min nasal cannula)
- Hypertension: 49%; diabetes: 31%
- Concomitant therapies:
  - Remdesivir: TCZ (33%) vs placebo (29%)
  - HCQ: TCZ (4%) vs placebo (4%)
  - Glucocorticoids: TCZ (11%) vs placebo (6%)

IQR: interquartile range; ICU: intensive care unit; TCZ: tocilizumab; HCQ: hydroxychloroquine



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. *NEJM*; Published online October 21, 2020. doi: 10.1056/NEJMoa2028836

RCT

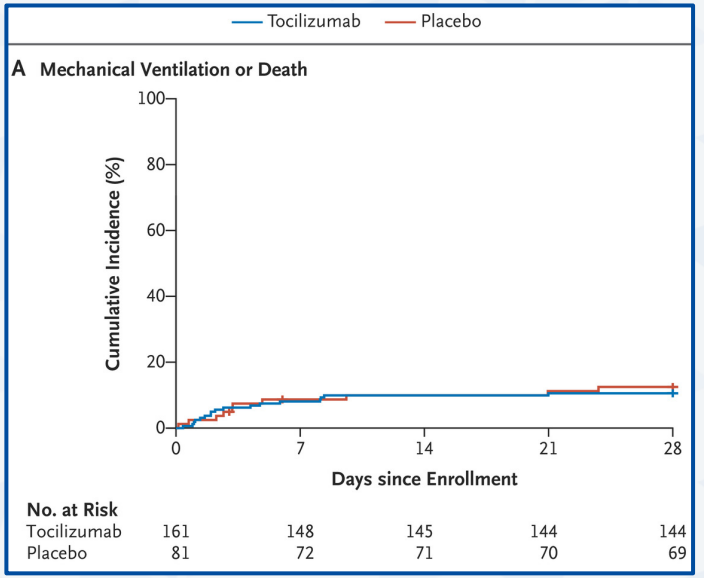
Results: Primary & Secondary Outcomes

Time to intubation or death:
- HR 0.83 (95% CI, 0.38 to 1.81; P=0.64)
- At 28 days: 17 vs 10

Time to clinical worsening
- HR 1.11 (95% CI, 0.59 to 2.10; P=0.73)
- At 28 days: 19.3% vs 17.4%

Time to discontinuation of supplemental oxygen:
- Median, 5.0 days vs 4.9 days
- HR 0.94 (95% CI, 0.67 to 1.30; P=0.69)
- At 28 days, 82.6% vs 84.9% were not receiving supplemental oxygen

All comparisons are tocilizumab vs placebo; HR: hazards ratio



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. *NEJM*; Published online October 21, 2020. doi: 10.1056/NEJMoa2028836

RCT

Results: Additional Outcomes

- Among 233 not in the ICU at enrollment, 15.9% vs 15.8% were admitted or died before ICU admission
- Among 19 patients who were intubated, median duration of mechanical ventilation: 15.0 days vs 27.9 days
- **Subgroup analyses:** greater risk of primary outcome in **patients > 65 years** (HR, 3.11; 95% CI, 1.36 to 7.10) and in those with **IL-6 > 40 pg/mL** (HR, 3.03; 95% CI, 1.34 to 6.83).
- **Safety:**
  - Neutropenia: 22 vs 1 (P=0.002)
  - Serious infections: 8.1% vs 17.3% (P=0.03)

All comparisons are tocilizumab vs placebo; HR: hazards ratio

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. *NEJM*; Published online October 21, 2020. doi: 10.1056/NEJMoa2028836

RCT

Take-Home Points

Strengths:

- Randomized controlled trial, multiple sites (7 Boston hospitals)
- Double-blinded, placebo-controlled

Limitations:

- Relatively short follow-up period
- Low primary event rate (12%)
- Small sample size, 80% power
- Imbalance of older patients in tocilizumab group

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. *NEJM*; Published online October 21, 2020. doi: 10.1056/NEJMoa2028836

RCT

COVACTA/EMPACTA

Study characteristic	Salvarani et al[1] (RCT-TCZ-COVID-19)	Hermine et al[2] (CORIMUNO-TOCI-1)	COVACTA[12]	EMPACTA[13]
Design				
Type	Randomized prospective	Randomized prospective	Randomized prospective	Randomized prospective
Blinded	No	No	Yes (double)	Yes (double)
Placebo-controlled	No	No	Yes	Yes
Enrollment				
No. of sites	24	9	67	69
Countries	Italy	France	Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US	Brazil, Kenya, Mexico, Peru, South Africa, US
No. of participants	126	131	450	389
No. tocilizumab treated	60[a]	63	225[b]	194[b]
Clinical severity[c]				
Moderate	No	No	No	No
Severe	Yes	Yes	Yes	Yes
Critical	No	No	Yes	No

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Parr JB. *JAMA Intern Med.* Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6557

Summary

- Optimal use of tocilizumab for patients with COVID-19 pneumonia has not yet been established.
- Several retrospective, observational studies demonstrate potential clinical efficacy and mortality benefit for tocilizumab, especially in severe and critically ill patients.
- However, only 2 of 5 currently available randomized controlled trials have met their primary efficacy outcomes.
- Fully published results from COVACTA, EMPACTA, and other RCTs are needed to inform clinical decisions.
- Currently, the National Institutes of Health and the Infectious Disease Society of America recommend against the use of tocilizumab unless in the context of a clinical trial.

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Parr JB. *JAMA Intern Med.* Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6557

Tocilizumab (Actemra®) & Other IL-6 Antagonists

An Updated Review of Pertinent Drug Information for SARS-CoV-2

Ana D. Vega, PharmD, BCIDP
Jackson Memorial Hospital
ana.vega@jhsmiami.org
@microbepharmd
November 18, 2020

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Overview: Case Reports

Study	Patients	Case Description	Main Conclusion
Michot JM, et. al. 2020	42-year-old man with metastatic sarcomatoid clear cell renal cell carcinoma	Admitted for fever, bone metastases; develops SARS-CoV-2 infection on hospital day 6; Receives two doses of TCZ (8mg/kg) on day 12; By day 12: supplemental oxygen discontinued, improvement in CT chest, afebrile.	+ TCZ may improve COVID-19-related respiratory failure
Zhang X, et. al. 2020	60-year-old man with history of multiple myeloma, clinically recovered	Initially admitted for SARS-CoV-2 infection, treated with antibiotics and umifenovir; readmitted 15 days later for chest tightness, treated with steroids; on day 9 receives TCZ 8mg/kg once. Three days later, chest tightness resolved.	+ TCZ may improve COVID-19-related respiratory failure
Radbel J, et. al. 2020	40-year-old man, no PMH	Admitted for hypoxemic respiratory failure and diagnosed with SARS-CoV-2. Requires MV on day 2; day 4 develops ARDS/septic shock and receives TCZ 400 mg IV once; day 5, STEMI; day 6 passes away	- TCZ not linked to positive outcome in patient with COVID-19-related respiratory failure
Radbel J, et. al. 2020	69-year-old woman with a PMH of type 2 DM, RA, and aplastic anemia	Diagnosed with SARS-CoV-2; on hospital day 2, develops respiratory failure requiring MV and septic shock. Receives TCZ 560 mg IV once; day 3: shock worsen; day 4: receives TCZ 700 mg IV once but passes away	- TCZ not linked to positive outcome in patient with COVID-19-related respiratory failure

PMH: past medical history TCZ: tocilizumab; CT: computer tomography; MV: mechanical ventilation; ARDS: acute respiratory distress syndrome; STEMI: ST-segment elevation myocardial infarction; DM: diabetes mellitus; RA: rheumatoid arthritis

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Michot JM, Albiges L, Chaput N, et al. *Annals of Oncology 2020*. https://doi.org/10.1016/j.annonc.2020.03.300.
Zhang X, Song K, Tong F, et al. *Blood Advances* 2020; 4(7): 1307-1310. doi:10.1182/bloodadvances.2020001907
Radbel J, Narayanan N, Bhatt Pinki. *CHEST* 2020. https://doi.org/10.1016/j.chest.2020.04.024

Overview: Case Series

Study	Population	Results	Conclusion
Xu X, et. al. 2020	N = 21; severe/critical	Within 24 hours, all patients defervesced; 75% lowered their O_2 intake; 90.5% had CT scan improvement	+ TCZ appeared to improve clinical symptoms
Luo P, et. al. 2020	N = 15; varying disease severities	Death: 20%; improvement: 6.7%; stability: 60%; aggravation: 13.3%	+/- A single dose of TCZ failed to improve disease activity in critically ill patients, however, repeated doses might be beneficial
Sciascia S, et. al. 2020	N = 63; severe	Mean PaO2/FiO2 increased significantly by day 14; TCZ within 6 days of admission associated with increased likelihood of survival (HR 2.2 95%CI 1.3–6.7, p<0.05); no ADE	+ Data suggests a promising role of TCZ in terms of efficacy and highlights safety profile

TCZ: tocilizumab; CT: computer tomography; TCZ: tocilizumab; HR: hazard ratio; ADE: adverse drug event

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Xu X, Mingfeng H, Tiantian L, et al. *PNAS* May 2020, 117 (20) 10970-10975; DOI:10.1073/pnas.2005615117
Luo P, Liu Y, Qiu L, et al. *J Med Virol* 2020; 1-5. doi: 10.1002/jmv.25801.
Sciascia S, Apra F, Baffa A, et al. *Clinical and Experimental Rheumatology* 2020; 38: 00-00. https://www.clinexprheumatol.org/article.asp?a=15723.

Overview: Retrospective Cohort Studies

Study	Population	Primary Outcome	Safety	Main Conclusion
Martinez-Sanz, et. al. 2020	N = 1229; moderate disease, non-ICU	Time-to-death	No analysis	+ TCZ linked to decreased time to mortality in patients with systemic inflammation (elevated CRP)
Biran, et. al. 2020	N = 764; severe, ICU	Time-to-hospital mortality	No significant difference between groups in infection rates	+ TCZ associated with a reduction in hospital-related mortality in those <65 and in those with elevated CRP
Guaraldi et. al. 2020 (TESEO)	N – 544; severe, 17% intubated	Composite of death or invasive mechanical ventilation	Significantly increased risk of secondary infections in the TCZ group	+ Significant reduction in risk of mechanical ventilation or death
Somers et. al. 2020 (Michigan Medicine)	N = 154; severe, intubated	Survival probability after intubation	Significantly increased risk of secondary infections in TCZ group	+ Survival probability was significantly higher among TCZ-treated patients
Gupta et. al. 2020 (STOP-COVID)	N = 3924; severe, ICU	Time-to-mortality	No analysis	+ TCZ-treated patients had a lower adjusted risk of death

TCZ: tocilizumab; CRP: C-reactive protein

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Martinez-Sanz J, Muriel A, Ron R, et al. *Clinical Microbiology and Infection* 2020. DOI: https://doi.org/10.1016/j.cmi.2020.09.021
Biran N, Ip A, Ahn J, et al. *The Lancet Rheumatology* 2020. 2(10):E603-612. https://doi.org/10.1016/S2665-9913(20)30277-0
Martinez-Sanz J, Muriel A, Ron R, et al. *Clinical Microbiology and Infection* 2020. DOI: https://doi.org/10.1016/j.cmi.2020.09.021
Somers EC, Eschenauer GA, Troost JP, et al. *Clin Infect Dis*; ciaa954, https://doi.org/10.1093/cid/ciaa954
Gupta S, Wang W, Hayek SS, et al. *JAMA Intern Med*. Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6252

RCT

RCT-TCZ-COVID-19

Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia

- Inclusion:
  - Adults at least 18 years old
  - PCR confirmed SARS-CoV-2
  - PaO_2/FiO_2 ratio 200-300 mmHg
  - Fever (>38 °C) during 2 days prior to randomization and/or serum CRP levels of ≥ 10 mg/dL and/or CRP doubled since admission
- Exclusion:
  - Invasive or non-invasive mechanical ventilation*
  - ICU admission
  - Tocilizumab hypersensitivity
  - Any condition preventing future admission to ICU

PCR: polymerase chain reaction; CRP: C-reactive protein
*After randomization, patients could receive non-invasive mechanical ventilation

- Primary outcome: composite of entry into the ICU with mechanical ventilation, death from all causes, or clinical aggravation (PaO_2/FiO_2 < 150 mm Hg), whichever came first.
- Secondary outcome: rate of patients admitted to the ICU with invasive mechanical ventilation at 14 and 30 days.

ICU: intensive care unit

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Salvarini C , Dolci G, Massari M, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615

RCT

Baseline Characteristics

Baseline Characteristic	Overall (n=126)	TCZ (n=60)	SOC (n=66)
Age (years), median (IQR)	60 (53-72)	61.5 (51.5-73.5)	60 (54-69)
Sex (male), n(%)	77 (61.1)	40 (66.7)	37 (56.1)
Obesity (BMI ≥ 30)	38 (32.2)	16 (28.1)	22 (36.1)
CRP, median (IQR), mg/dL	8.2 (3.7-13.5)	10.5 (5.0-14.6)	6.5 (3.2-11.8)
IL-6, median (IQR), pg/dL	42.1 (20.6-74.9)	50.4 (28.3-93.2)	34.3 (19.0-59.3)
Hydroxychloroquine, n(%)	115 (91.3)	53 (88.3)	62 (93.9)
Antiretrovirals, n(%)*	52 (41.3)	21 (35.0)	31 (47.0)
Azithromycin, n(%)	26 (20.6)	10 (16.7)	16 (24.2)

TCZ: tocilizumab; SOC: standard of care; IQR: interquartile range; BMI: body mass index; CRP: C-reactive protein; IL-6: interleukin 6
* darunavir/cobicistat, darunavir/ritonavir, or lopinavir/ritonavir

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Salvarini C , Dolci G, Massari M, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615

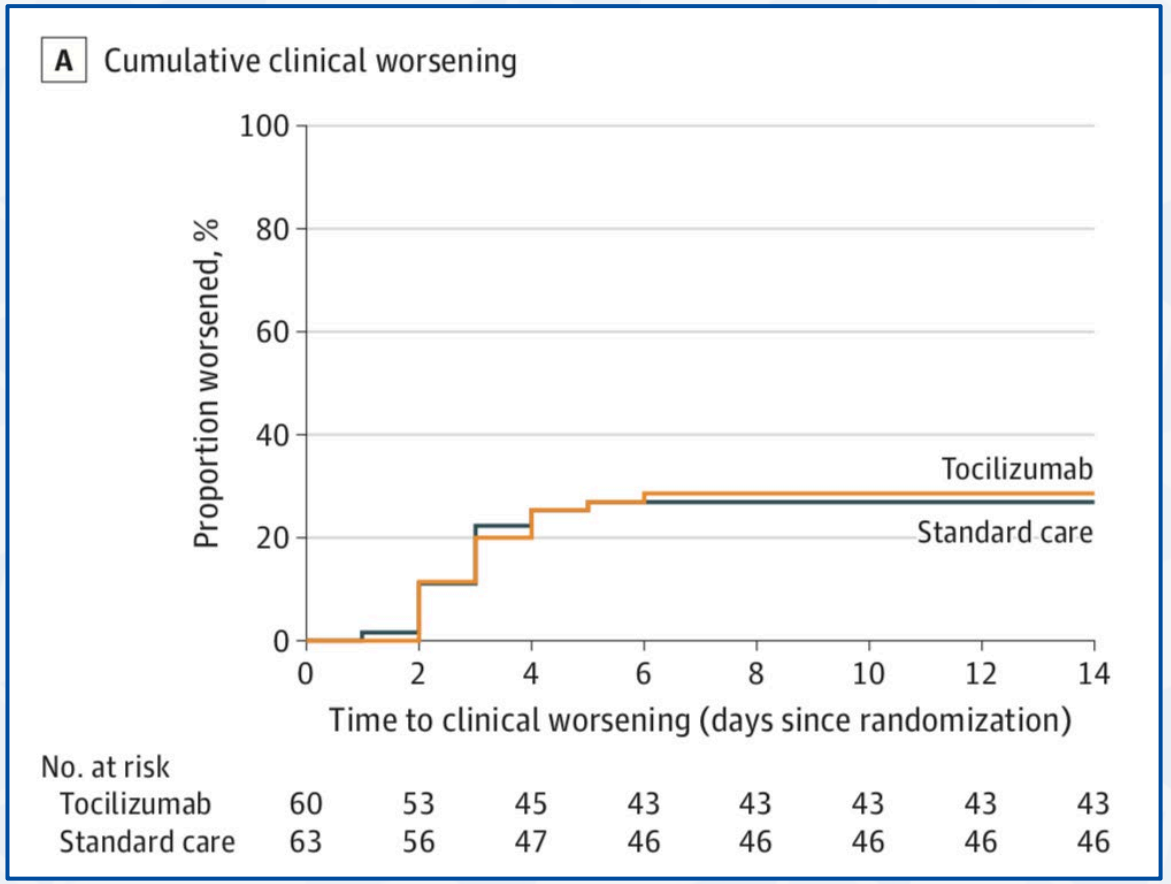
RCT

Outcomes: ITT Population

- ICU admission within 14 days: n=14
  - 10.0% vs 7.9% (RR, 1.26; 95% CI, 0.41-3.91)
- Mortality at 14 days:
  - 1.7% vs 1.6% (RR, 1.05; 95% CI, 0.07-16.4)
- Clinical worsening:
  - 28.3% vs 27.0% (RR, 1.05; 95% CI, 0.59-1.86; p=0.87)
  - No difference in time to event

All comparisons are tocilizumab vs standard of care, within 14 days of randomization

Kaplan-Meier Estimates of Cumulative Clinical Worsening



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Salvarini C , Dolci G, Massari M, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615; ITT: intention-to-treat

RCT

Take-Home Points

Strengths:

- Randomized controlled trial, multiple sites (24)

Limitations:

- Prematurely interrupted after an interim analysis for futility (did not meet power); small sample size
- Open-label, not placebo-controlled (bias primary outcome assessment)
- Low overall mortality rate (external validity)
- Exclusion criteria introduced sampling bias
- Composite endpoint with components of varying clinical significance
- **Patients in the control arm allowed to receive tocilizumab as rescue therapy (23.3%)**

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Salvarini C , Dolci G, Massari M, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6615

RCT

CORIMUNO-19-TOCI-1

Effect of Tocilizumab vs Usual Care in Adults Hospitalized with COVID-19 and Moderate or Severe Pneumonia

- Primary outcome:
  - Scores higher than 5 on the WHO-CPS on day 4
  - Survival without need of any ventilation on day 14
- Secondary outcomes:
  - WHO-CPS scores at day 7 and day 14
  - Overall survival
  - Time to discharge
  - Time to oxygen supply independency
  - Biological factors (i.e. CRP)
  - Adverse events

WHO-CPS: World Health Organization 10-point Clinical Progression Scale; CRP: C-reactive protein

WHO Clinical Progression Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820
WHO Working Group on the Clinical Characterization and Management of COVID-19 infection. *Lancet Infect Dis* 2020; 20: e192–97. doi: 10.1016/ S1473-3099(20)30483-7

RCT

Population

- Inclusion:
  - Adults at least 18 years old
  - PCR confirmed SARS-CoV-2 and/or typical CT chest findings
  - Moderate or severe pneumonia: WHO-CPS score of 5 receiving at least 3L/min oxygen but without HFO, NIV, or MV
- Exclusion:
  - Hypersensitivity to TCZ
  - Pregnancy
  - Documented bacterial infection
  - Patients with any of following laboratory results:
    - ANC < 1.0×10^9/L or less
    - Platelets < 50 g/L.

PCR: polymerase chain reaction; CT: computed tomography; HFO: high-flow oxygen; NIV: non-invasive ventilation; MV: mechanical ventilation; TCZ: tocilizumab; ANC: absolute neutrophil count

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

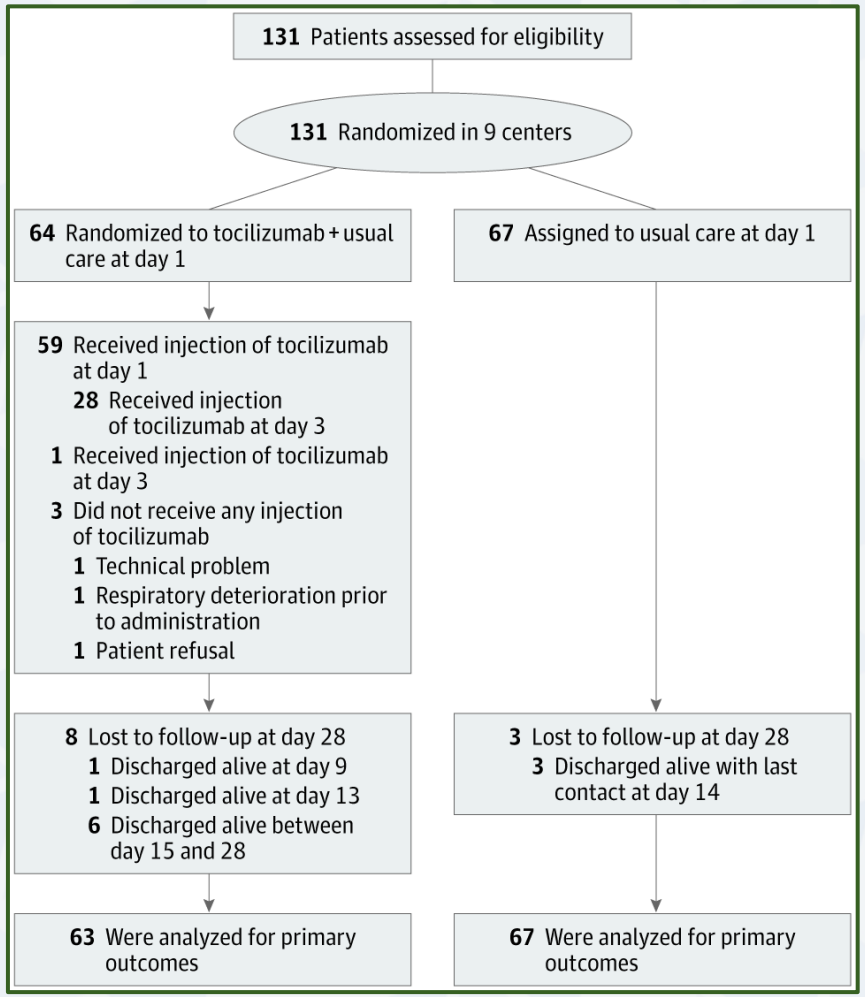
Results

Baseline Characteristics:

- No significant between-group differences at enrollment
- Median age: 64 years (IQR, 57.1-74.3); 88 (68%) men
- Median BMI ~27
- PCR-confirmed infection in 89% (TCZ) and 90% (SOC)
- Oxygen need at baseline: median 5L/min with median SpO2 of 95%
- Most common comorbidities: diabetes; chronic cardiac disease
- Concomitant medications, TCZ vs SOC:
  - Antiviral drugs (lopinavir/ritonavir): 7(11%) vs 16 (24%)
  - Glucocorticoids: 21 (33%) vs 41 (61%)
  - Immunomodulators: 1 (anakinra) vs 4 (anakinra, n = 3; eculizumab, n = 1)

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Study Flowchart



Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

Primary Outcome

eTable 3. Day 4 outcome.

In the protocol the D4 primary outcome is defined as a WHO-CPS score ≤ 5 at day 4, and patients with a new DNR at, or before, day 4 where considered as with a WHO-CPS score > 5. Results are presented as proportions with a WHO-CPS score > 5, so that an effective treatment would result in a risk reduction.

	Tocilizumab	UC	Absolute Risk Difference	Adjusted Odds Ratio
N	63	67		
N (%) WHO-CPS > 5	12 (19%)	19 (28%)		
Posterior Median	19.7%	28.8%	-9.0%	0.57
90% CrI			-21.0 to +3.1	0.28 to 1.15
95% CrI	11.3 to 30.5	19.0 to 40.1	-23.3 to +5.5	0.24 to 1.32
Posterior probabilities*				
P(Any benefit)			0.890	0.905
P(Moderate or greater benefit)			0.684	0.823

* P(Any benefit)=P(ARD < 0) or P(OR < 1), P(Moderate or greater benefit) = P(ARD < -5.5%) or P(OR < 0.85)

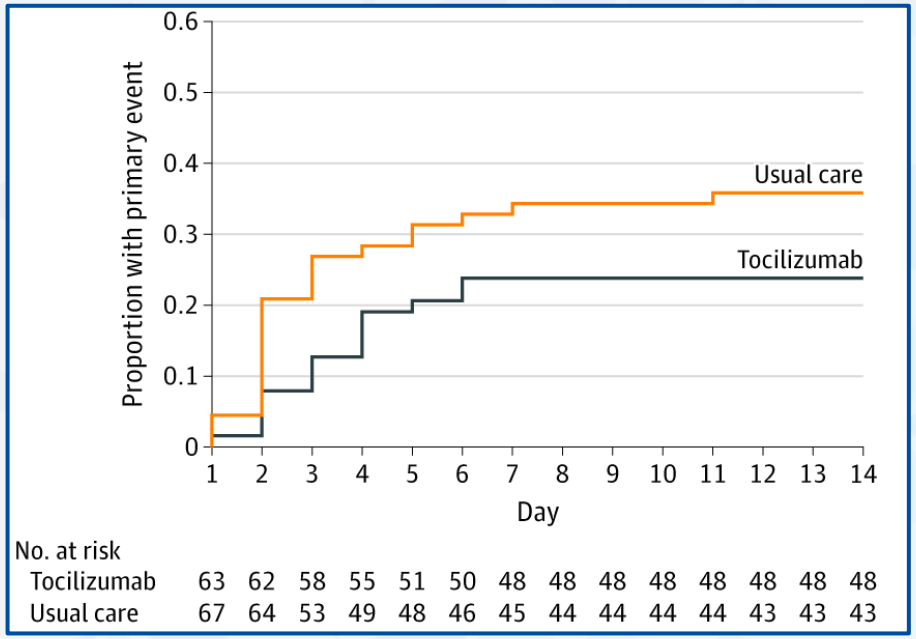
SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

Primary Outcome

Probability of death or MV, HFO, NIV at Day 14



HFO: high-flow oxygen; MV: mechanical ventilation; NIV: noninvasive ventilation.

Variable	Tocilizumab (n = 63)	UC (n = 67)	Difference (95% CI)
Primary outcome by day 14, No.	15	24	
Cumulative incidence, % (95% CI)	24 (13 to 34)	36 (23 to 46)	−12 (−28 to 4)
First event, No.			
NIV/HFO	8	13	
MV	3	8	
Death/DNR order	4	3	

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

Take-Home Points

Strengths:

- Randomized controlled trial, multiple sites (9)
- Bayesian modeling of primary outcome
- Suggests that tocilizumab may improve clinical progression at 14 days; no effect on mortality

Limitations:

- Small sample size, open-label
- Short follow-up period
- Not all patients had PCR-confirmed disease (subgroup analyses completed)
- More patients in the SOC arm received glucocorticoids, despite randomization
- OR and HR adjusted only for age and center for primary/secondary outcomes
- Missing data considered primary outcome failure
- Do not resuscitate orders considered events

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Hermine O, Mariette X, Tharaux P-L, et al. *JAMA Intern Med*; Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6820

RCT

BACC Bay Tocilizumab Trial

Efficacy of Tocilizumab in Patients Hospitalized with COVID-19

- Intervention: randomly assigned (2:1) to tocilizumab (8 mg/kg) or placebo
- Primary outcome:
  - Time to intubation or death
- Secondary outcomes:
  - Time to clinical worsening*
  - Time to discontinuation of supplemental oxygen

PCR: polymerase-chain reaction; IgM: immunoglobulin M; CRP: C-reactive protein; LDH: lactate dehydrogenase

*Defined as an increase by at least 1-2 points on a 7-point scale from discharge/ready for discharge (=1) to death (=7)

- Inclusion:
  - Adults 19-85 years old
  - PCR or serum IgM antibody + SARS-CoV-2
  - At least one:
    - CRP > 50 m/L, ferritin > 500 ng/mL, a d-dimer > 1000 ng/mL, or LDH > 250 U/L
  - At least two of the following signs:
    - fever (>38°C) within 72h of enrollment
    - Pulmonary infiltrates
    - Need for supplemental oxygen (for SpO2 >92%)
- Exclusion:
  - Supplemental oxygen > 10L/min
  - Recent treatment with biologic agent
  - Diverticulitis

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. *NEJM*; Published online October 21, 2020. doi: 10.1056/NEJMoa2028836

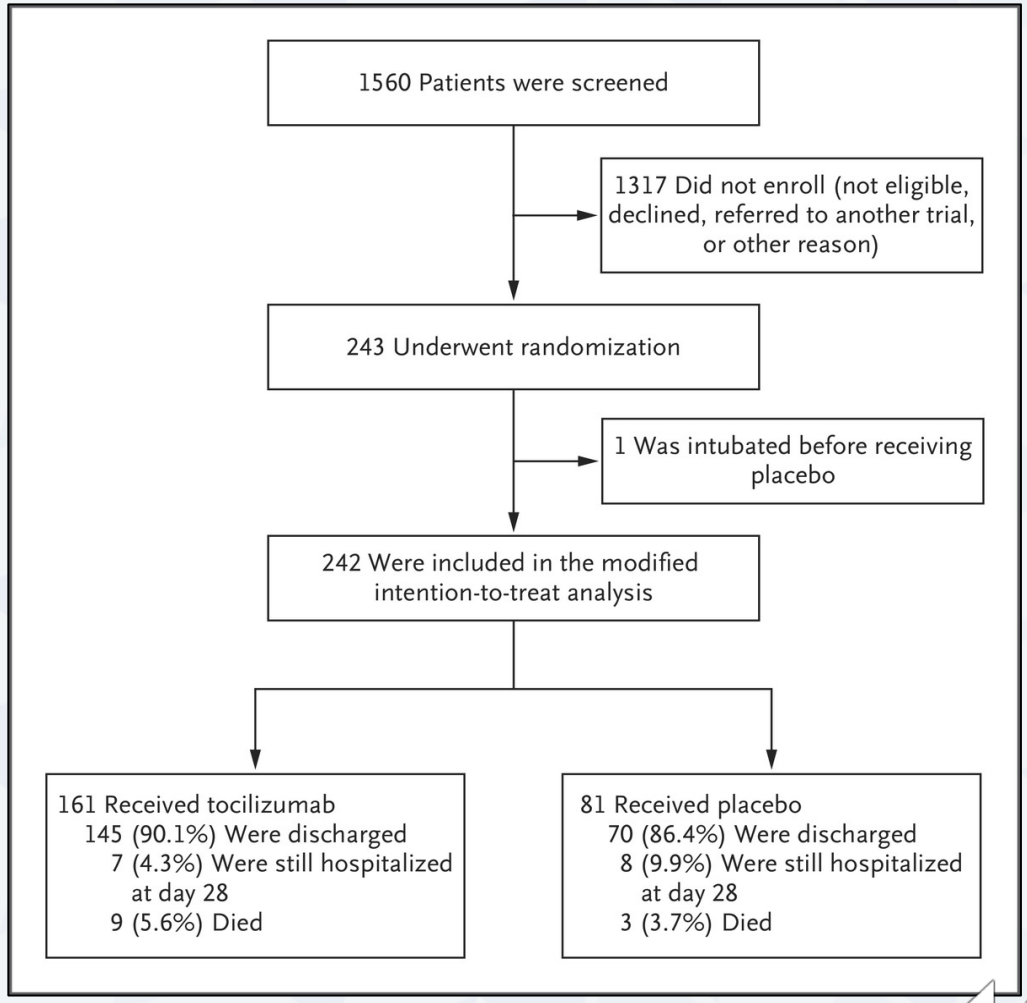
RCT

Results

Baseline Characteristics:

- Median age (years): 59.8 (IQR 45.3-69.4)
- 58.0% male; 45% Hispanic/Latino
- 80% hospitalized in non-ICU hospital wards and receiving supplemental oxygen (≤6 L/min nasal cannula)
- Hypertension: 49%; diabetes: 31%
- Concomitant therapies:
  - Remdesivir: TCZ (33%) vs placebo (29%)
  - HCQ: TCZ (4%) vs placebo (4%)
  - Glucocorticoids: TCZ (11%) vs placebo (6%)

IQR: interquartile range; ICU: intensive care unit; TCZ: tocilizumab; HCQ: hydroxychloroquine



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. *NEJM*; Published online October 21, 2020. doi: 10.1056/NEJMoa2028836

RCT

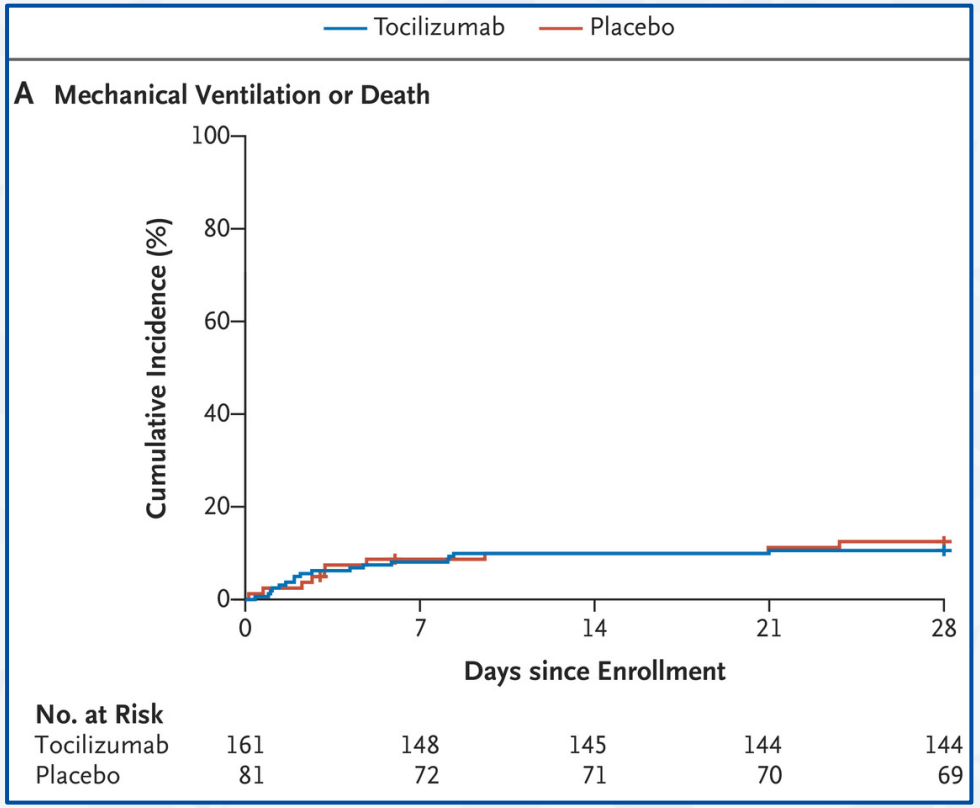
Results: Primary & Secondary Outcomes

Time to intubation or death:
- HR 0.83 (95% CI, 0.38 to 1.81; P=0.64)
- At 28 days: 17 vs 10

Time to clinical worsening
- HR 1.11 (95% CI, 0.59 to 2.10; P=0.73)
- At 28 days: 19.3% vs 17.4%

Time to discontinuation of supplemental oxygen:
- Median, 5.0 days vs 4.9 days
- HR 0.94 (95% CI, 0.67 to 1.30; P=0.69)
- At 28 days, 82.6% vs 84.9% were not receiving supplemental oxygen

All comparisons are tocilizumab vs placebo; HR: hazards ratio



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. *NEJM*; Published online October 21, 2020. doi: 10.1056/NEJMoa2028836

RCT

Take-Home Points

Strengths:

- Randomized controlled trial, multiple sites (7 Boston hospitals)
- Double-blinded, placebo-controlled

Limitations:

- Relatively short follow-up period
- Low primary event rate (12%)
- Small sample size, 80% power
- Imbalance of older patients in tocilizumab group

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Stone JH, Frigault MJ, Serling-Boyd NJ, et al. *NEJM*; Published online October 21, 2020. doi: 10.1056/NEJMoa2028836

RCT

COVACTA/EMPACTA

Study characteristic	Salvarani et al[1] (RCT-TCZ-COVID-19)	Hermine et al[2] (CORIMUNO-TOCI-1)	COVACTA[12]	EMPACTA[13]
Design				
Type	Randomized prospective	Randomized prospective	Randomized prospective	Randomized prospective
Blinded	No	No	Yes (double)	Yes (double)
Placebo-controlled	No	No	Yes	Yes
Enrollment				
No. of sites	24	9	67	69
Countries	Italy	France	Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US	Brazil, Kenya, Mexico, Peru, South Africa, US
No. of participants	126	131	450	389
No. tocilizumab treated	60[a]	63	225[b]	194[b]
Clinical severity[c]				
Moderate	No	No	No	No
Severe	Yes	Yes	Yes	Yes
Critical	No	No	Yes	No

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Parr JB. *JAMA Intern Med.* Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6557

Relevant Clinical Trials*

Sarilumab

- Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19 (NCT04315298) – COMPLETE; did not meet primary outcome (data unpublished)
- Sarilumab for Patients With Moderate COVID-19 Disease: A Randomized Controlled Trial With a Play-The-Winner Design (NCT04359901)
- **SARCOVID**: Efficacy of Subcutaneous Sarilumab in Hospitalised Patients With Moderate-severe COVID-19 Infection (NCT04357808)

Siltuximab

- Efficacy and Safety of Siltuximab vs. Corticosteroids in Hospitalized Patients With COVID-19 Pneumonia (NCT04329650)
- **SISCO**: An Observational Case-control Study of the Use of Siltuximab in ARDS Patients Diagnosed With COVID-19 Infection (NCT04322188)
- **COV-AID**: Treatment of COVID-19 Patients With Anti-interleukin Drugs [phase 3 observational study] (NCT04330638)

Tocilizumab

- **COVACTA**: A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (NCT04320615)
- **EMPACTA:** A Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia (NCT04372186)
- **REMDACTA:** 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 (NCT04409262)
- Tocilizumab for Prevention of Respiratory Failure in Patients With Severe COVID-19 Infection (NCT04377659)
- **COVIDOSE**: Tocilizumab to Prevent Clinical Decompensation in Hospitalized, N[illegible] critically Ill Patients With COVID-1[illegible] Pneumonitis (NCT04331795)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

*Not all-inclusive; only included US clinical trials for Tocilizumab; only recruiting trials

Summary

- Optimal use of tocilizumab for patients with COVID-19 pneumonia has not yet been established.
- Several retrospective, observational studies demonstrate potential clinical efficacy and mortality benefit for tocilizumab, especially in severe and critically ill patients.
- However, only 2 of 5 currently available randomized controlled trials have met their primary efficacy outcomes.
- Fully published results from COVACTA, EMPACTA, and other RCTs are needed to inform clinical decisions.
- Currently, the National Institutes of Health and the Infectious Disease Society of America recommend against the use of tocilizumab unless in the context of a clinical trial.

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Parr JB. *JAMA Intern Med.* Published online October 20, 2020. doi:10.1001/jamainternmed.2020.6557