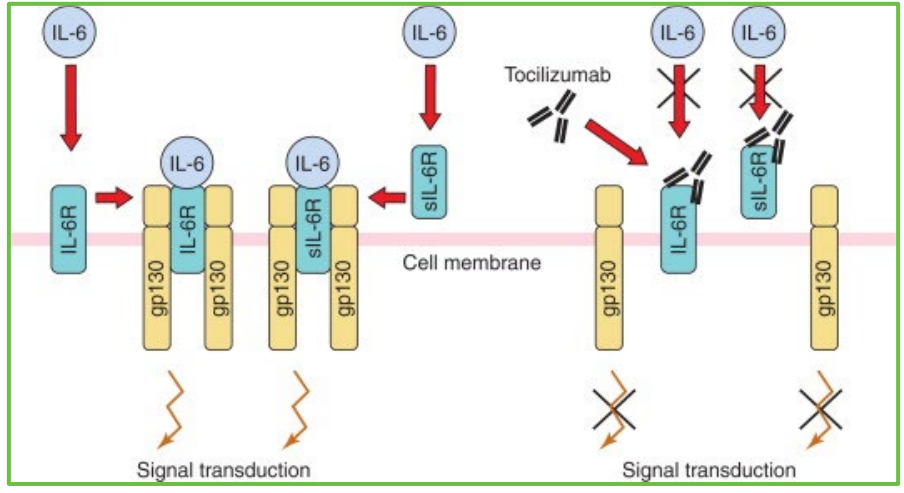
Mechanism of Action

- 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

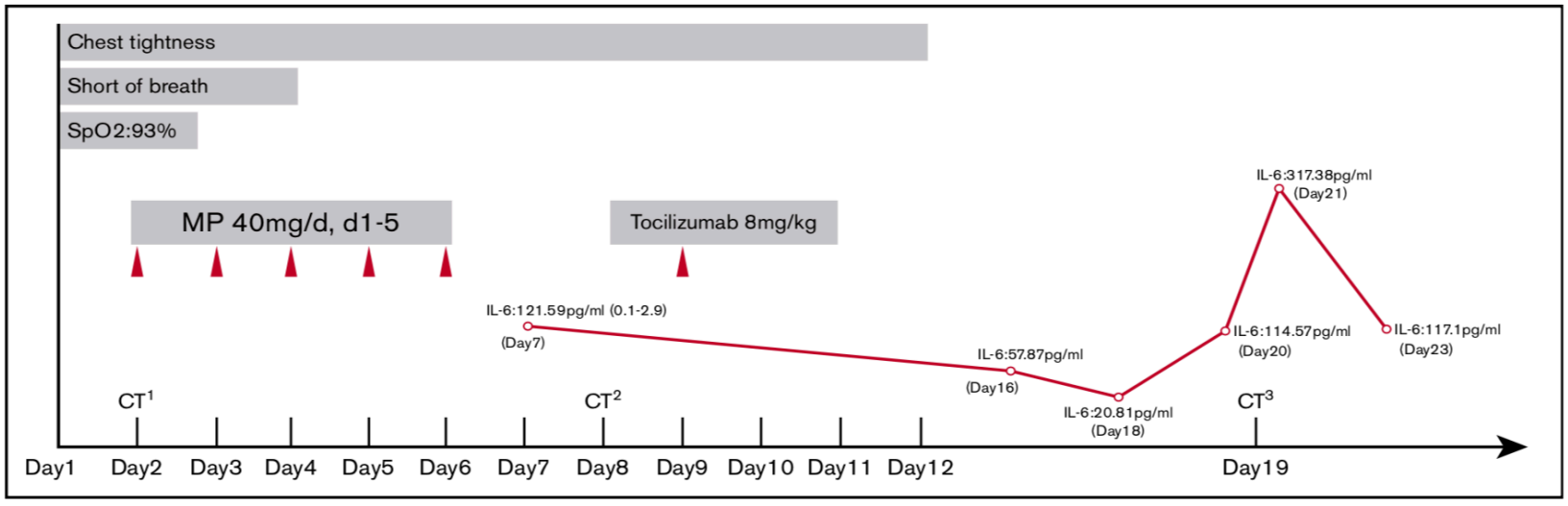


Figure 2. Timeline of symptoms, IL-6 level, and treatment after admission. CT^1, first CT scan; CT^2, second CT scan; CT^3, third CT scan; MP, methylprednisolone; SpO_2, peripheral oxygen saturation.

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	...	...	MP 20 mg	MP 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/ritonavir; 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 airway pressure

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

Relevant Clinical Trials

Tocilizumab

- **COVACTA**: A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (NCT04320615)
- Tocilizumab for the Treatment of Cytokine Release Syndrome in Patients With COVID-19 (NCT04361552)
- Efficacy of Tocilizumab on Patients With COVID-19 (NCT04356937)
- Tocilizumab for Prevention of Respiratory Failure in Patients With Severe COVID-19 Infection (NCT04377659)
- **COVIDOSE**: Tocilizumab to Prevent Clinical Decompensation in Hospitalized, Non-critically Ill Patients With COVID-19 Pneumonitis (NCT04331795)

Sarilumab

- Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19 (NCT04315298)
- 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)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

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

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS