Tocilizumab (Actemra®) & Other IL-6 Antagonists

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

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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
• Pathogenesis of previous coronaviruses (SARS, MERS) suggests a cytokine storm is involved.

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

- 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

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: 3\(^{rd}\) CT chest now with improvement in lesions; patient discharged

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GGO: ground-glass opacities; MP: methylprednisolone

Tocilizumab Case Reports

Figure 2. Timeline of symptoms, IL-6 level, and treatment after admission. CT¹, first CT scan; CT², second CT scan; CT³, third CT scan; MP, methylprednisolone; SpO₂, peripheral oxygen saturation.

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

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”

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*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

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

Table 1: The characteristics of COVID-19 patients treated with TCZ

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

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

*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

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
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/mm³, platelets are <150,000/mm³, 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/mm³, platelets ≥50,000/mm³, and hemoglobin <17 g/dL
- Risk of infection is also a consideration with this agent

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• 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
## Data Available: Sarilumab

### U.S. Sarilumab Trial – Phase 2 Efficacy Results

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT (REDUCTION IN C-REACTIVE PROTEIN)</th>
<th>Placebo (n=77)</th>
<th>Kevzara 200 mg (n=136)</th>
<th>Kevzara 400 mg (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% change from baseline in CRP</td>
<td>-21%</td>
<td>-77%</td>
<td>-79%</td>
</tr>
<tr>
<td>(Patients with high baseline IL-6, where data was available)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### EXPLORATORY CLINICAL ENDPOINTS IN “CRITICAL” GROUP

<table>
<thead>
<tr>
<th>Died or “On a ventilator”</th>
<th>Placebo (n=44)</th>
<th>Kevzara 200 mg (n=94)</th>
<th>Kevzara 400 mg (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>12 (27%)</td>
<td>34 (36%)</td>
<td>20 (23%)</td>
</tr>
<tr>
<td>On a ventilator</td>
<td>12 (27%)</td>
<td>9 (10%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>18 (41%)</td>
<td>48 (51%)</td>
<td>52 (59%)</td>
</tr>
<tr>
<td>(Achieved ≥2 point improvement on 7-point scale)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off oxygenation</td>
<td>18 (41%)</td>
<td>40 (43%)</td>
<td>51 (58%)</td>
</tr>
<tr>
<td>Discharged</td>
<td>18 (41%)</td>
<td>37 (39%)</td>
<td>47 (53%)</td>
</tr>
</tbody>
</table>

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”

*Five patients received a second dose.

ARDS: acute respiratory distress syndrome; CRP: C-reactive protein; CPAP: continuous positive airway pressure

Relevant Clinical Trials

**Tocilizumab**
- **COVACTA**: A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia ([NCT04320615](https://clinicaltrials.gov/ct2/show/NCT04320615))
- Tocilizumab for the Treatment of Cytokine Release Syndrome in Patients With COVID-19 ([NCT04361552](https://clinicaltrials.gov/ct2/show/NCT04361552))
- Efficacy of Tocilizumab on Patients With COVID-19 ([NCT04356937](https://clinicaltrials.gov/ct2/show/NCT04356937))
- Tocilizumab for Prevention of Respiratory Failure in Patients With Severe COVID-19 Infection ([NCT04377659](https://clinicaltrials.gov/ct2/show/NCT04377659))
- **COVIDOSE**: Tocilizumab to Prevent Clinical Decompensation in Hospitalized, Non-critically Ill Patients With COVID-19 Pneumonitis ([NCT04331795](https://clinicaltrials.gov/ct2/show/NCT04331795))

**Sarilumab**
- Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19 ([NCT04315298](https://clinicaltrials.gov/ct2/show/NCT04315298))
- Sarilumab for Patients With Moderate COVID-19 Disease: A Randomized Controlled Trial With a Play-The-Winner Design ([NCT04359901](https://clinicaltrials.gov/ct2/show/NCT04359901))
- **SARCOVID**: Efficacy of Subcutaneous Sarilumab in Hospitalised Patients With Moderate-severe COVID-19 Infection ([NCT04357808](https://clinicaltrials.gov/ct2/show/NCT04357808))

**Siltuximab**
- Efficacy and Safety of Siltuximab vs. Corticosteroids in Hospitalized Patients With COVID-19 Pneumonia ([NCT04329650](https://clinicaltrials.gov/ct2/show/NCT04329650))
- **SISCO**: An Observational Case-control Study of the Use of Siltuximab in ARDS Patients Diagnosed With COVID-19 Infection ([NCT04322188](https://clinicaltrials.gov/ct2/show/NCT04322188))
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 trials are ongoing for Tocilizumab and Sarilumab in COVID-19