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
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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\(^1\)
- Pathogenesis of previous coronaviruses (SARS, MERS) suggests a cytokine storm is involved.\(^2,3\)

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Tocilizumab Case Reports

Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure¹

- 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

- 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
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.
### 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

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

**Purpose**

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

**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
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
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

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

Data Available: Sarilumab

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

### EXPLORATORY CLINICAL ENDPOINTS IN “CRITICAL” GROUP

<table>
<thead>
<tr>
<th>Died or “On a ventilator”</th>
<th>(n=44)</th>
<th>(n=94)</th>
<th>(n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>24 (55%)</td>
<td>43 (46%)</td>
<td>28 (32%)</td>
</tr>
<tr>
<td>On a ventilator</td>
<td>12 (27%)</td>
<td>34 (36%)</td>
<td>20 (23%)</td>
</tr>
</tbody>
</table>

Clinical improvement (Achieved ≥2 point improvement on 7-point scale)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>(n=44)</th>
<th>(n=94)</th>
<th>(n=88)</th>
</tr>
</thead>
<tbody>
<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>

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\(^1\) Clinical improvement defined as ≥2 point improvement on a 7-point scale.
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*

**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)

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

- **2,047 patients screened**
- **818 missing data**
- **1,229 patients analyzed**
- **Tocilizumab: 260**
- **No Tocilizumab: 969**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group (n = 969)</th>
<th>Tocilizumab (n = 260)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (IQR)</strong></td>
<td>68 (57 - 80)</td>
<td>65 (55 - 76)</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>574 (59)</td>
<td>191 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Female</td>
<td>395 (41)</td>
<td>69 (27)</td>
<td></td>
</tr>
<tr>
<td><strong>Past medical history, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hypertension</td>
<td>227 (23)</td>
<td>44 (17)</td>
<td>0.042</td>
</tr>
<tr>
<td>- Diabetes</td>
<td>233 (24)</td>
<td>47 (18)</td>
<td></td>
</tr>
<tr>
<td><strong>Vital signs at admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Peripheral O₂ saturation (%)</td>
<td>94 (92-96)</td>
<td>91 (86-94)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Baseline laboratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ALC (cells/µL), median (IQR)</td>
<td>1050 (770 - 1440)</td>
<td>890 (630 - 1225)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>523 (408 - 664)</td>
<td>669 (566 - 829)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- LDH (U/L), median (IQR)</td>
<td>64 (27 - 122)</td>
<td>113 (64 - 220)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>27 (7 - 60)</td>
<td>70 (26 - 182)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>- CRP (mg/L), median (IQR)</td>
<td>64 (27 - 122)</td>
<td>113 (64 - 220)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>- IL-6 (pg/mL), median (IQR)</td>
<td>27 (7 - 60)</td>
<td>70 (26 - 182)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>


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Martinez-Sanz J, et. al. 199x339

Martinez-Sanz J, Sanz J, et. al. 199x339

Martinez-Sanz J, Sanz J, et. al. 199x339
## Results

### Unadjusted Outcomes for the Overall Cohort

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Control group (n=969)</th>
<th>Tocilizumab (n=260)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ICU length of stay (days), median (IQR)</td>
<td>8 (5-10)</td>
<td>13 (10-18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU admission, n (%)</td>
<td>32 (3)</td>
<td>50 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU length of stay (days), median (IQR)</td>
<td>2 (1-3)</td>
<td>6 (2-11)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>120 (12)</td>
<td>61 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU or mortality, n (%)</td>
<td>120 (12)</td>
<td>66 (25)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
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

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)

Time to death, CRP ≥ 150 mg/L\(^2\)
aHR 0.34, 95% CI 0.17-0.71, p=0.005

**Secondary Outcome**

**Time to ICU/death**

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**

aHR 1.41, 95% CI 0.77-2.58, p=0.264

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)

**Time to ICU/death, CRP ≥ 150 mg/L**

aHR 0.39, 95% CI 0.19-0.80, p=0.011

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
## Baseline Characteristics

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

*Propensity score-matched cohort (n = 630)
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)
**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

### Variables Associated with Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab, yes vs no</td>
<td>0.64 (0.47-0.87)</td>
<td>0.0040</td>
</tr>
<tr>
<td>Age, ≥ 65 vs &lt; 65 years</td>
<td>2.00 (1.58-2.53)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender, female vs male</td>
<td>0.68 (0.53-0.86)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Hypertension, yes vs no</td>
<td>1.44 (1.13-1.84)</td>
<td>0.0031</td>
</tr>
<tr>
<td>CRP &gt; 15 mg/dL, missing vs no</td>
<td>2.11 (1.49-2.98)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intubation, yes vs no</td>
<td>8.78 (2.79-27.61)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

**Multivariable Cox Regression Model by Age**

### Age < 65 (n=307)

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

### Age ≥ 65 (n=312)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab, yes vs no</td>
<td>0.71 (0.48-1.04)</td>
<td>0.73</td>
</tr>
<tr>
<td>Gender, female vs male</td>
<td>0.74 (0.55-0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td>Hypertension, yes vs no</td>
<td>1.39 (1.00-1.91)</td>
<td>0.047</td>
</tr>
<tr>
<td>Steroids, missing vs no</td>
<td>1.93 (1.15-3.24)</td>
<td>0.013</td>
</tr>
<tr>
<td>CRP ≥ 15 mg/dL, missing vs no</td>
<td>2.31 (1.46-3.65)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>
# Multivariable Cox Regression Model by C-Reactive Protein (CRP) Level

## CRP < 15 mg/dL (n=272)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab, yes vs no</td>
<td>0.92 (0.57-1.48)</td>
<td>0.73</td>
</tr>
<tr>
<td>Age, ≥ 65 vs &lt; 65 years</td>
<td>1.83 (1.28-2.62)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender, female vs male</td>
<td>0.59 (0.41-0.85)</td>
<td>0.0041</td>
</tr>
<tr>
<td>Hypertension, yes vs no</td>
<td>1.89 (1.26-2.85)</td>
<td>0.0023</td>
</tr>
<tr>
<td>Intubation, yes vs no</td>
<td>9.14 (2.24-37.33)</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

## CRP ≥ 15 mg/dL (n=286)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab, yes vs no</td>
<td>0.48 (0.30-0.77)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Age, ≥ 65 vs &lt; 65 years</td>
<td>1.97 (1.39-2.78)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Oxygenation &lt;94%, missing vs no</td>
<td>0.17 (0.04-0.81)</td>
<td>0.026</td>
</tr>
<tr>
<td>Intubation, yes vs no</td>
<td>8.56 (1.18-62.03)</td>
<td>0.034</td>
</tr>
</tbody>
</table>
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
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
### TESEO Study

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


<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>SQ Toci (n=91)</th>
<th>IV Toci (n=88)</th>
<th>Overall (n=179)</th>
<th>SOC (n = 365)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 (55-73)</td>
<td>63 (54-72)</td>
<td>64 (54-72)</td>
<td>69 (57-78)</td>
<td>0.0064</td>
</tr>
<tr>
<td>P/F (mmHg)</td>
<td>199 (123-262)</td>
<td>145 (102-229)</td>
<td>169 (106-246)</td>
<td>277 (191-345)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SOFA Score</td>
<td>2 (1-3)</td>
<td>3 (2-4)</td>
<td>3 (2-4)</td>
<td>2 (0-3)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Days from sx onset</td>
<td>8 (5-10)</td>
<td>4 (3-8)</td>
<td>7 (4-10)</td>
<td>5 (2-9)</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

**Outcomes**

<table>
<thead>
<tr>
<th>Follow-up (days)</th>
<th>12 (6-17)</th>
<th>13 (7-18)</th>
<th>12 (6-17)</th>
<th>8 (4-14)</th>
<th>&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7 (8%)</td>
<td>6 (7%)</td>
<td>13 (7%)</td>
<td>73 (20%)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

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

1351 COVID-19+ screened

544 eligible

807 excluded: did not meet severe definition

179 Tocilizumab 91 subcutaneous 88 intravenous

365 standard of care (SOC)* only

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

---

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

*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.
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.
**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
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

Michigan COVID-19 Rapid Response Registry*

All patients admitted for COVID-19 (PCR+), n=484

Study Cohort
Mechanically ventilated patients with COVID-19, N=154

Excluded
- Infant (1)
- Enrolled in sarilumab RCT (34)
- Not mechanically ventilated (293)
- Died <28h on ventilator (2), n=330

*All Michigan Medicine patients with confirmed or suspected COVID, positive SARS-CoV-2 test; PCR: polymerase-chain reaction

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 O₂
- 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
Balancing After the Inverse Probability of Treatment Weighting (IPTW)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-IPTW</th>
<th>Post-IPTW</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tocilizumab-treated</td>
<td>tocilizumab-untreated</td>
<td>$p$-value</td>
</tr>
<tr>
<td>Age, Mean (SD)</td>
<td>53 (16.0)</td>
<td>61 (14.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>16</td>
<td>25</td>
<td>0.24</td>
</tr>
<tr>
<td>Chronic pulmonary disease, %</td>
<td>10</td>
<td>27</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic renal disease, %</td>
<td>35</td>
<td>49</td>
<td>0.12</td>
</tr>
<tr>
<td>Therapeutic anticoagulation, %</td>
<td>82</td>
<td>68</td>
<td>0.08</td>
</tr>
<tr>
<td>Ferritin, Mean (SD)</td>
<td>1854 (2525)</td>
<td>2199 (2513)</td>
<td>0.47</td>
</tr>
<tr>
<td>LDH, Mean (SD)</td>
<td>746 (403)</td>
<td>712 (569)</td>
<td>0.78</td>
</tr>
<tr>
<td>AST, Mean (SD)</td>
<td>101 (88)</td>
<td>183 (652)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

(n=116)
<table>
<thead>
<tr>
<th>Study Models</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full cohort: n=154</strong></td>
</tr>
<tr>
<td>Model A: Demographic adjusted analyses</td>
</tr>
<tr>
<td>Tocilizumab treated n=78</td>
</tr>
<tr>
<td><strong>IPTW subset with complete data (no missing labs): n=116</strong></td>
</tr>
<tr>
<td>Model B: Demographic + IPTW adjusted analyses</td>
</tr>
<tr>
<td>IPTW balanced n=49</td>
</tr>
<tr>
<td><strong>IPTW-MI (with imputed data for missing labs): n=154</strong></td>
</tr>
<tr>
<td>Model C: Demographic + IPTW-MI adjusted analyses</td>
</tr>
<tr>
<td>IPTW balanced, with imputed values n=78</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

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

TCZ: Tocilizumab; MV: mechanical ventilation
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

• 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)

OR (95% CI)* estimates of the association between 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

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


Society of Infectious Diseases Pharmacists
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

**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)

Statistical Plan

Standardized Differences Before and After Applying Inverse Probability Weighting

• 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

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

4485 Critically ill patients with laboratory-confirmed COVID-19 admitted to ICUs from March 4 to May 10, 2020
561 Excluded from analysis
267 Enrolled in a placebo-controlled trial with an IL-6 antagonist
203 Admitted to the ICU ≥7 d after hospital admission
63 Had an AST or ALT >500 U/L on ICU admission
20 Received an IL-6 antagonist other than tocilizumab
8 Received tocilizumab before ICU admission

3924 Categorized by receipt of tocilizumab within 48 h of ICU admission

433 Received tocilizumab within 2 d of ICU admission
229 Treated on day 1 of ICU admission (53%)
204 Treated on day 2 of ICU admission (47%)

3491 Did not receive tocilizumab within 2 d of ICU admission
433 Included in the primary analysis
3491 Included in the primary analysis
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%

*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
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

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

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.

### Results


---

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

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of deaths / No. of patients (%)</th>
<th>Adjusted HR (95% CI)</th>
<th>Favors tocilizumab</th>
<th>Favors no tocilizumab</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td>125/433 (28.9)</td>
<td>1419/3491 (40.6)</td>
<td>0.71 (0.56-0.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without censoring at discharge</td>
<td>125/433 (28.9)</td>
<td>1419/3491 (40.6)</td>
<td>0.72 (0.56-0.93)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Unweighted Cox model</td>
<td>125/433 (28.9)</td>
<td>1419/3491 (40.6)</td>
<td>0.75 (0.62-0.91)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Nested target trial approach</td>
<td>125/433 (28.9)</td>
<td>1419/3491 (40.6)</td>
<td>0.64 (0.50-0.81)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Exclusion of moribund patients²</td>
<td>119/426 (27.9)</td>
<td>1339/3392 (39.5)</td>
<td>0.71 (0.55-0.92)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Adjustment for No. of ICU beds</td>
<td>125/433 (28.9)</td>
<td>1419/3491 (40.6)</td>
<td>0.71 (0.55-0.90)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

#### Subgroups

- **Age, y**
  - <60: 57/240 (23.8) vs 366/1425 (25.7) 0.80 (0.57-1.12)
  - ≥60: 68/193 (35.2) vs 1053/2066 (51.0) 0.66 (0.49-0.89)

- **Sex**
  - Male: 88/299 (29.4) vs 925/2165 (42.7) 0.71 (0.52-0.97)
  - Female: 37/134 (27.6) vs 494/1326 (37.3) 0.72 (0.58-1.08)

- **Time from symptom onset to ICU admission, d**
  - ≤3: 15/58 (25.9) vs 429/835 (51.4) 0.41 (0.23-0.74)
  - >3: 110/379 (29.3) vs 990/2696 (37.3) 0.85 (0.65-1.11)

- **PaO2/FiO2 ratio on ICU admission**
  - ≥200: 48/188 (25.5) vs 581/1834 (31.7) 0.88 (0.58-1.35)
  - <200: 65/205 (31.7) vs 663/1122 (50.2) 0.59 (0.41-0.83)

- **Vasopressor treatment on ICU admission**
  - No: 68/254 (26.8) vs 769/2126 (36.2) 0.76 (0.53-1.07)
  - Yes: 57/179 (31.8) vs 650/1365 (47.6) 0.66 (0.47-0.93)

- **Corticosteroid treatment on ICU admission**
  - No: 91/352 (25.9) vs 1189/3051 (38.0) 0.71 (0.53-0.96)
  - Yes: 34/81 (42.0) vs 230/440 (52.3) 0.68 (0.46-0.99)

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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
## Summary: Retrospective Studies

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

TCZ: tocilizumab; CRP: C-reactive protein
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
  • PaO₂/FiO₂ 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

• Primary outcome: composite of entry into the ICU with mechanical ventilation, death from all causes, or clinical aggravation (PaO₂/FiO₂ < 150 mm Hg), whichever came first.

• Secondary outcome: rate of patients admitted to the ICU with invasive mechanical ventilation at 14 and 30 days.

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

ICU: intensive care unit

## Baseline Characteristics

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

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
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.
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%)
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
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 < $1.0 \times 10^9$/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
• 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
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)
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.

<table>
<thead>
<tr>
<th></th>
<th>Tocilizumab</th>
<th>UC</th>
<th>Absolute Risk Difference</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>63</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%) WHO-CPS &gt; 5</td>
<td>12 (19%)</td>
<td>19 (28%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior Median</td>
<td>19.7%</td>
<td>28.8%</td>
<td>-9.0%</td>
<td>0.57</td>
</tr>
<tr>
<td>90% Crl</td>
<td>-21.0 to +3.1</td>
<td>0.28 to 1.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% Crl</td>
<td>-23.3 to +5.5</td>
<td>0.24 to 1.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior probabilities*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(Any benefit)</td>
<td>0.890</td>
<td>0.905</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(Moderate or greater benefit)</td>
<td>0.684</td>
<td>0.823</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

**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

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)
**Clinical Improvement Scale**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Discharged (or &quot;ready for discharge&quot; as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or &lt;= 2L supplemental oxygen)</td>
</tr>
<tr>
<td>2</td>
<td>Non-ICU hospital ward (or &quot;ready for hospital ward&quot;) not requiring supplemental oxygen</td>
</tr>
<tr>
<td>3</td>
<td>Non-ICU hospital ward (or &quot;ready for hospital ward&quot;) requiring supplemental oxygen</td>
</tr>
<tr>
<td>4</td>
<td>ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen</td>
</tr>
<tr>
<td>5</td>
<td>ICU, requiring intubation and mechanical ventilation</td>
</tr>
<tr>
<td>6</td>
<td>ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy)</td>
</tr>
<tr>
<td>7</td>
<td>Death</td>
</tr>
</tbody>
</table>

**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
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

1560 Patients were screened

1317 Did not enroll (not eligible, declined, referred to another trial, or other reason)

243 Underwent randomization

1 Was intubated before receiving placebo

242 Were included in the modified intention-to-treat analysis

161 Received tocilizumab
- 145 (90.1%) Were discharged
- 7 (4.3%) Were still hospitalized at day 28
- 9 (5.6%) Died

81 Received placebo
- 70 (86.4%) Were discharged
- 8 (9.9%) Were still hospitalized at day 28
- 3 (3.7%) Died
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
**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
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
<table>
<thead>
<tr>
<th>Study characteristic</th>
<th>Salvarani et al(^1) (RCT-TZC-COVID-19)</th>
<th>Hermine et al(^2) (CORMUNO-TOCI-1)</th>
<th>COVACTA(^{1,2})</th>
<th>EMPACTA(^{1,3})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Randomized prospective</td>
<td>Randomized prospective</td>
<td>Randomized prospective</td>
<td>Randomized prospective</td>
</tr>
<tr>
<td>Blinded</td>
<td>No</td>
<td>No</td>
<td>Yes (double)</td>
<td>Yes (double)</td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of sites</td>
<td>24</td>
<td>9</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>Countries</td>
<td>Italy</td>
<td>France</td>
<td>Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US</td>
<td>Brazil, Kenya, Mexico, Peru, South Africa, US</td>
</tr>
<tr>
<td>No. of participants</td>
<td>126</td>
<td>131</td>
<td>450</td>
<td>389</td>
</tr>
<tr>
<td>No. tocilizumab treated</td>
<td>60(^a)</td>
<td>63</td>
<td>225(^b)</td>
<td>194(^b)</td>
</tr>
<tr>
<td><strong>Clinical severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Severe</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Critical</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
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.
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
### Overview: Case Reports

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Case Description</th>
<th>Main Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michot JM, et. al. 2020</td>
<td>42-year-old man with metastatic sarcomatoid clear cell renal cell carcinoma</td>
<td>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.</td>
<td>+ TCZ may improve COVID-19-related respiratory failure</td>
</tr>
<tr>
<td>Zhang X, et. al. 2020</td>
<td>60-year-old man with history of multiple myeloma, clinically recovered</td>
<td>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.</td>
<td>+ TCZ may improve COVID-19-related respiratory failure</td>
</tr>
<tr>
<td>Radbel J, et. al. 2020</td>
<td>40-year-old man, no PMH</td>
<td>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</td>
<td>- TCZ not linked to positive outcome in patient with COVID-19-related respiratory failure</td>
</tr>
<tr>
<td>Radbel J, et. al. 2020</td>
<td>69-year-old woman with a PMH of type 2 DM, RA, and aplastic anemia</td>
<td>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</td>
<td>- TCZ not linked to positive outcome in patient with COVID-19-related respiratory failure</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu X, et. al. 2020</td>
<td>N = 21; severe/critical</td>
<td>Within 24 hours, all patients defervesced; 75% lowered their O₂ intake; 90.5% had CT scan improvement</td>
<td>+ TCZ appeared to improve clinical symptoms</td>
</tr>
<tr>
<td>Luo P, et. al. 2020</td>
<td>N = 15; varying disease severities</td>
<td>Death: 20%; improvement: 6.7%; stability: 60%; aggravation: 13.3%</td>
<td>+/- A single dose of TCZ failed to improve disease activity in critically ill patients, however, repeated doses might be beneficial</td>
</tr>
<tr>
<td>Sciascia S, et. al. 2020</td>
<td>N = 63; severe</td>
<td>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&lt;0.05); no ADE</td>
<td>+ Data suggests a promising role of TCZ in terms of efficacy and highlights safety profile</td>
</tr>
</tbody>
</table>

TCZ: tocilizumab; CT: computer tomography; TCZ: tocilizumab; HR: hazard ratio; ADE: adverse drug event
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Safety</th>
<th>Main Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez-Sanz, et. al. 2020</td>
<td>N = 1229; moderate disease, non-ICU</td>
<td>Time-to-death</td>
<td>No analysis</td>
<td>+ TCZ linked to decreased time to mortality in patients with systemic inflammation (elevated CRP)</td>
</tr>
<tr>
<td>Biran, et. al. 2020</td>
<td>N = 764; severe, ICU</td>
<td>Time-to-hospital mortality</td>
<td>No significant difference between groups in infection rates</td>
<td>+ TCZ associated with a reduction in hospital-related mortality in those &lt;65 and in those with elevated CRP</td>
</tr>
<tr>
<td>Guaraldi et. al. 2020</td>
<td>N – 544; severe, 17% intubated</td>
<td>Composite of death or invasive mechanical ventilation</td>
<td>Significantly increased risk of secondary infections in the TCZ group</td>
<td>+ Significant reduction in risk of mechanical ventilation or death</td>
</tr>
<tr>
<td>Somers et. al. 2020</td>
<td>N = 154; severe, intubated</td>
<td>Survival probability after intubation</td>
<td>Significantly increased risk of secondary infections in TCZ group</td>
<td>+ Survival probability was significantly higher among TCZ-treated patients</td>
</tr>
<tr>
<td>Gupta et. al. 2020</td>
<td>N = 3924; severe, ICU</td>
<td>Time-to-mortality</td>
<td>No analysis</td>
<td>+ TCZ-treated patients had a lower adjusted risk of death</td>
</tr>
</tbody>
</table>

TCZ: tocilizumab; CRP: C-reactive protein

**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
  - PaO₂/FiO₂ 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

- **Primary outcome:** composite of entry into the ICU with mechanical ventilation, death from all causes, or clinical aggravation (PaO₂/FiO₂ < 150 mm Hg), whichever came first.

- **Secondary outcome:** rate of patients admitted to the ICU with invasive mechanical ventilation at 14 and 30 days.

---

PCR: polymerase chain reaction; CRP: C-reactive protein

*After randomization, patients could receive non-invasive mechanical ventilation

**ICU:** intensive care unit

---

## Baseline Characteristics

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

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
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

![Kaplan-Meier graph showing cumulative clinical worsening](image-url)

- No difference in time to event

**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%)**
**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 Clinical Progression Scale**

<table>
<thead>
<tr>
<th>Patient State</th>
<th>Descriptor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>Uninfected; no viral RNA detected</td>
<td>0</td>
</tr>
<tr>
<td>Ambulatory mild disease</td>
<td>Asymptomatic; viral RNA detected</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Symptomatic; independent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Symptomatic; assistance needed</td>
<td>3</td>
</tr>
<tr>
<td>Hospitalised: moderate disease</td>
<td>Hospitalised; no oxygen therapy*</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Hospitalised; oxygen by mask or nasal prongs</td>
<td>5</td>
</tr>
<tr>
<td>Hospitalised: severe diseases</td>
<td>Hospitalised; oxygen by NIV or high flow</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Intubation and mechanical ventilation, pO₂/FIO₂ ≥ 150 or SpO₂/FIO₂ ≥ 200</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Mechanical ventilation pO₂/FIO₂ &lt; 150 (SpO₂/FIO₂ &lt; 200) or vasopressors</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Mechanical ventilation pO₂/FIO₂ &lt; 150 and vasopressors, dialysis, or ECMO</td>
<td>9</td>
</tr>
<tr>
<td>Dead</td>
<td>Dead</td>
<td>10</td>
</tr>
</tbody>
</table>

WHO-CPS: World Health Organization 10-point Clinical Progression Scale; CRP: C-reactive protein
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.
**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)
# Primary Outcome

**eTable 3. Day 4 outcome.**

In the protocol the D4 primary outcome is defined as a WHO-CPS score \( \leq 5 \) 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.

<table>
<thead>
<tr>
<th></th>
<th>Tocilizumab</th>
<th>UC</th>
<th>Absolute Risk Difference</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>63</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%) WHO-CPS &gt; 5</td>
<td>12 (19%)</td>
<td>19 (28%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior Median</td>
<td>19.7%</td>
<td>28.8%</td>
<td>-9.0%</td>
<td>0.57</td>
</tr>
<tr>
<td>90% Crl</td>
<td>-21.0 to +3.1</td>
<td>0.28 to 1.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% Crl</td>
<td>-23.3 to +5.5</td>
<td>0.24 to 1.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior probabilities*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(Any benefit)</td>
<td>0.890</td>
<td>0.905</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(Moderate or greater benefit)</td>
<td>0.684</td>
<td>0.823</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* \( P(\text{Any benefit}) = P(\text{ARD} < 0) \) or \( P(\text{OR} < 1) \), \( P(\text{Moderate or greater benefit}) = P(\text{ARD} < -5.5\%) \) or \( P(\text{OR} < 0.85) \)
Primary Outcome

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

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

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

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
**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

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

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

---

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
<table>
<thead>
<tr>
<th>Study characteristic</th>
<th>Salvarani et al.¹ (RCT-TCZ-COVID-19)</th>
<th>Hermine et al.² (CORIMUNO-TOCI-1)</th>
<th>COVACTA³⁴</th>
<th>EMPACTA³⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Randomized prospective</td>
<td>Randomized prospective</td>
<td>Randomized prospective</td>
<td>Randomized prospective</td>
</tr>
<tr>
<td>Blinded</td>
<td>No</td>
<td>No</td>
<td>Yes (double)</td>
<td>Yes (double)</td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of sites</td>
<td>24</td>
<td>9</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>Countries</td>
<td>Italy</td>
<td>France</td>
<td>Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US</td>
<td>Brazil, Kenya, Mexico, Peru, South Africa, US</td>
</tr>
<tr>
<td>No. of participants</td>
<td>126</td>
<td>131</td>
<td>450</td>
<td>389</td>
</tr>
<tr>
<td>No. tocilizumab treated</td>
<td>60ᵃ</td>
<td>63</td>
<td>225ᵇ</td>
<td>194ᵇ</td>
</tr>
<tr>
<td><strong>Clinical severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Severe</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Critical</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Relevant Clinical Trials*

**Sarilumab**
- Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19 ([NCT04315298](https://clinicaltrials.gov/show/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](https://clinicaltrials.gov/show/NCT04359901))
- **SARCOVID**: Efficacy of Subcutaneous Sarilumab in Hospitalised Patients With Moderate-severe COVID-19 Infection ([NCT04357808](https://clinicaltrials.gov/show/NCT04357808))

**Siltuximab**
- Efficacy and Safety of Siltuximab vs. Corticosteroids in Hospitalized Patients With COVID-19 Pneumonia ([NCT04329650](https://clinicaltrials.gov/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/show/NCT04322188))
- **COV-AID**: Treatment of COVID-19 Patients With Anti-interleukin Drugs [phase 3 observational study] ([NCT04330638](https://clinicaltrials.gov/show/NCT04330638))

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

*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.