Tocilizumab Literature Review: COVID-19 Clinical Advisory Group Update
March 2021

Background:
- Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that acts as an interleukin 6 (IL-6) receptor antagonist and is approved for the use of CAR-T associated cytokine release syndrome. Due to similarities in the clinical presentation of CAR-T cytokine release syndrome and the hyperinflammatory state of severe COVID-19, interest in tocilizumab for severe COVID-19 developed early in the pandemic. To a lesser extent, other IL-6 agents have also been investigated (e.g. sarilumab).
- Although several observational studies have suggested mortality benefit, data from randomized controlled trials to date have primarily shown no benefit from IL-6 antagonists.
- Emerging data from the REMAP-CAP, EMPACTA, and RECOVERY trials indicate positive benefits especially in critically ill patients.

Data Summary:
- Randomized Controlled Trials¹⁻⁸
  - Findings from the RECOVERY trial conflict with peer-reviewed randomized trials which did not show a benefit of tocilizumab in 28-day mortality or clinical improvement in patients with severe COVID-19. Patients in these studies tended to have moderate-to-severe illness not requiring ICU care.
  - Two recent randomized controlled trials suggest early use of tocilizumab improve clinical outcomes including survival among critically ill patients when used in combination with dexamethasone.
- Systematic Review and Meta-Analysis¹,⁹
  - Meta-analysis of 8 RCTs (RECOVERY, REMAP-CAP, EMPACTA, TOCIBRAS, COVACTA, BACC, RCT-T CZ-COVID-19, CORIMUNO) revealed a significant mortality benefit. However, when outlier of RECOVERY trial was removed, this mortality benefit was no longer observed.
  - Lower mortality was observed among 10 retrospective observational studies (9 of high quality). No differences in mechanical ventilation, mortality after mechanical ventilation, or ICU admission.
- Retrospective Cohorts¹⁰⁻¹⁷
  - Several observational studies have suggested mortality benefit in critically ill patients but at the cost of increased secondary bacterial infections.
- Guideline Recommendations:
  - IDSA guidelines: Among hospitalized adults with progressive severe (SpO₂ ≤94% on room air, including patients on supplemental oxygen) or critical COVID-19 (patients on mechanical ventilation, ECMO, or with end organ dysfunction as is seen in sepsis/septic shock (e.g. ARDS)) who have elevated markers of systemic inflammation (i.e. CRP ≥ 75 mg/L), the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e. steroids) rather than standard of care alone. (Last updated February 17, 2021).
    - Patients, particularly those who respond to steroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab.
  - NIH guidelines: For patients who are within 24 hours of admission to the intensive care unit (ICU) and require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO₂/30 L/min oxygen flow), there are insufficient data to recommend either for or against the use of tocilizumab or sarilumab for the treatment of COVID-19 (Last updated February 3, 2021).
    - Some Panel members would administer a single dose of tocilizumab (8 mg/kg of actual body weight, up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure.
    - For patients who do not require ICU-level care or are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of tocilizumab or sarilumab for the treatment of COVID-19, except in a clinical trial (BIIa).
  - NHS interim guidance: Eligible patients include COVID positive/highly suspected patients who are receiving (or have completed a course of) dexamethasone or an equivalent corticosteroids AND with a C-reactive protein level of at least 75 mg/L; AND an oxygen saturation of <92% on room air OR requirement for supplemental oxygen; OR If an IL-6 inhibitor has not been already administered for COVID-19 during this admission and within 24-48 hours of commencement of respiratory support (e.g. high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation). (Last updated February 22, 2021).

Recommendations:
- Further studies are needed to confirm results of recent RCTs. In the interim, tocilizumab can be considered for severe or critically ill adult patients with confirmed COVID-19 AND oxygen saturation <92% on room air OR requirement for supplemental oxygen AND evidence of systemic inflammation (i.e. CRP ≥ 75 mg/L) OR who are exhibiting rapid progression of respiratory failure AND within 24 hours of commencing respiratory support (e.g. high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation)
  - Dosing: 800 mg if weight >90kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8 mg/kg if weight ≤40 kg x1 dose only, in addition to dexamethasone (concomitant use required). Tocilizumab monotherapy is not recommended and should not be considered a substitute for corticosteroids.
  - Exclusion criteria: evidence of active TB or other non-COVID infection (bacterial, fungal, or viral), presumption of imminent death, condition or treatment resulting in ongoing immunsuppression including neutropenia (ANC <500), pregnancy, active liver disease or ALT/AST >5 x ULN, PLT< 50.

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Recommendations:
- Further studies are needed to confirm results of recent RCTs. In the interim, tocilizumab can be considered for severe or critically ill adult patients with confirmed COVID-19 AND oxygen saturation <92% on room air OR requirement for supplemental oxygen AND evidence of systemic inflammation (i.e. CRP ≥ 75 mg/L) OR who are exhibiting rapid progression of respiratory failure AND within 24 hours of commencing respiratory support (e.g. high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation)
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  - Exclusion criteria: evidence of active TB or other non-COVID infection (bacterial, fungal, or viral), presumption of imminent death, condition or treatment resulting in ongoing immunsuppression including neutropenia (ANC <500), pregnancy, active liver disease or ALT/AST >5 x ULN, PLT< 50.
Randomized controlled, open-label platform trial of 4116 hospitalized patients with COVID-19 across 131 UK hospitals

Randomized to tocilizumab (n=2022; 8 mg/kg, max 800 mg) or usual care (n=2094). A second dose could be given 12 to 24 hours later if, condition had not improved at physician discretion

Included

- Hospitalized adults ≥ clinically suspected or laboratory confirmed COVID AND
- Oxygen saturation <92% on air OR requiring oxygen therapy AND
- Evidence of systemic inflammation (CRP ≥ 75 mg/L)

Exclusion

- Known hypersensitivity to tocilizumab or use contraindicated
- Evidence of active tuberculosis infection or clear evidence of active bacterial, fungal, viral, or other non-COVID infection

Patient selection:

- Mean age 63.6 (SD 13.7), median CRP 143 [IQR 107-204], 82% concomitant corticosteroids
- Male (66%), White (67%), DM (28%)
- At randomization, 562 (13.5%) patients were receiving invasive mechanical ventilation, 1686 (41%) non-invasive respiratory support (i.e. high-flow nasal oxygen, CPAP, and non-invasive ventilation), and 1868 (45%) “simple” oxygen therapy, 9 (0.2%) not receiving oxygen

Primary outcome:

- Treatment with tocilizumab was associated with a significant reduction in 28-day mortality (33% vs 29%, 0.86; [95% CI: 0.77-0.96], p=0.0066)

Secondary outcome:

- Tocilizumab treated patients had a higher probability of discharge from hospital alive within 28 days (1.22; [95% CI: 1.12-1.34], p<0.0001)
- Treatment effect was largest for concomitant corticosteroid use (p=0.01)
- An exploratory analysis showed that the effects of tocilizumab on 28-day mortality were similar for those randomized ≤2 or >2 days since hospitalization (p=0.86)
- Among those not receiving invasive mechanical ventilation at baseline, patients treated with tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (33% vs. 38%, 0.85; [95% CI: 0.76-0.93], p=0.0005)
- No significant difference in receipt of non-invasive (p=0.94) or invasive mechanical ventilation (p=0.07) among those not on respiratory support at baseline
- No significant difference in successful cessation of invasive mechanical ventilation among those on invasive mechanical ventilation at randomization (p=0.64)
- Tocilizumab use was associated with less incidence of renal dialysis or hemofiltration (5% vs 7%, p=0.02)

Adverse events:

- No excess deaths related to infection were reported
- Serious adverse reactions believed to be related tocilizumab (n=1 otitis externa, n=1 Staphylococcus aureus bacteremia, n=1 lung 278 abscess) all of which resolved with standard treatment

Meta-analysis including all RCTs to date

- Seven RCTs (REMAP-CAP, EMPACTA, TOCIBRAS, COVACTA, BACC, RCT-TCZ-COVID-19, CORIMUNO) did not reveal a significant mortality benefit (0.91; [95%CI: 0.72-1.14]).
- After RECOVERY trial was included in analysis, a mortality benefit was significant (0.87; [95%CI: 0.79-0.96], p=0.005). (Large sample size contributed highest number of deaths in analysis). Heterogeneity I²=20%

Limitations:

- Pre-publication of interim data (not yet peer reviewed)
- Open-label design
- Median time to symptom onset not discussed
- Unknown benefit in hypoxic patients with a CRP <75 mg/L

Tocilizumab reduced mortality, increased the chances of successful hospital discharge, and reduced the risk of requiring invasive mechanical ventilation in hospitalized patients with severe COVID-19

Greatest benefit seen using both IL-6 receptor antagonists and corticosteroids (vs. monotherapy) and those receiving respiratory support but not mechanical ventilation at baseline

Meta-analysis of 8 RCT to date reveal a significant mortality benefit. However, when outlier of RECOVERY trial was removed, this mortality benefit was no longer observed.

Open-label, randomized, adaptive trial of 803 adult ICU patients

Randomized to tocilizumab (n=353; 8 mg/kg, max 800 mg) or sarilumab (n=48; 400 mg) or standard of care (n=402).

A second dose of tocilizumab could be given 12-24 hours at discretion of physician (29%)

Included

- Critically ill adults ≥18 years admitted to the ICU with suspected or confirmed COVID
- Respiratory or cardiovascular support
- Presumption of imminent death

Primary outcome:

- Respiratory and cardiovascular support-free days up to day 21
  - Median organ-support free days with tocilizumab (10; IQR -1,16) and sarilumab therapy (11; IQR 0,16) compared to control (0: IQR -1,15)
  - Adjusted odds ratio were 1.64 ([95% CI: 1.25-2.14]) and 1.76 (95% CI: 1.17-2.91) for tocilizumab and sarilumab, respectively; yielding >99.9% and 95% posterior odds of superiority

Primary Hospital Survival:

- Hospital mortality was 28.0% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab and 35.8% (142/397) for control
- Median adjusted odds ratio for hospital survival were lower for IL-6 antagonists (tocilizumab (1.64; CI: 1.14-2.35), sarilumab (2.01; CI: 1.18-4.71), Control 1
- Treatment effect was greater with corticosteroids vs. any intervention alone

Secondary outcome:

- 90 Day Survival: tocilizumab (1.59; CI: 1.24-2.05), sarilumab (1.82; CI: 1.22-3.38), Control 1

In critically ill COVID-19 adult patient requiring respiratory or cardiovascular support, treatment with IL-6 antagonists improved clinical outcomes and survival

Similar effects were seen in all CRP subgroups

Greatest benefit seen using both IL-6 receptor antagonists and corticosteroids in critical ill population (vs. monotherapy)

Limitations:

- Pre-publication (not yet peer reviewed)
- Open-label design
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<td>Salama, January 2021 [EMPACTA](^\text{4}) LOE 1b, n=388</td>
<td>Randomized, double-blind, placebo-controlled, phase 3 study of 388 patients hospitalized with COVID-19 and evidence of pneumonia NOT on mechanical ventilation</td>
<td>- Time to ICU Discharge: tocilizumab (1.42; CI: 1.18-1.70), sarilumab (1.64; CI: 1.21-2.45), Control 1  - Time to Hospital Discharge: tocilizumab (1.41; CI: 1.18-1.70), sarilumab (1.60; CI: 1.17-2.40), Control 1  - Improvement in WHO ordinal scale at day 14: tocilizumab (1.83; CI: 1.40-2.41), sarilumab (1.86; CI: 1.22-2.91), Control 1</td>
<td>- Not all outcomes reported (11 missing)  - Trial is ongoing, long-term outcomes may differ from short-term, preliminary outcomes</td>
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### Study: EMPACTA

| Prior participation in REMAP-CAP within 90 days | Admitted to ICU >24 hours earlier | Known immune suppression | Enrolled in another trial | Additional exclusion criteria specific to immune modulation therapy

#### Patient Selection:
- All but 3 received respiratory support (high-flow oxygen (28.8%), non-invasive (41.5%), and invasive mechanical ventilation (29.4%)
- Median Time to enrollment from hospital admission (1.2 days), from ICU admission (13.4 hours)
- Mean age 61.4, Male (72.7%), White (72.4%), Median BMI 30.5, Median APACHE II 12.5
- Concurrent corticosteroid 93.8% (610/654) and remdesivir use 32.8% (265/807)

#### Inclusion criteria:
- COVID-19 and evidence of pneumonia NOT on mechanical ventilation
- Randomized to tocilizumab (n=249; 8 mg/kg, max 800 mg) or placebo (n=128).

#### A second dose of tocilizumab could be given 8-24 hours if clinical signs or symptoms worsened or did not approve (i.e. sustained fever or worsening ordinal scale scores)

#### Exclusion:
- Hospitalized adults ≥18 years with confirmed COVID
- Oxygen Saturation below 94% on RA
- Active TB or suspected active bacterial, fungal or viral treatment
- Known immunosuppression
- Oral antirejection or immunomodulatory therapy within past 3 months
- ALT or AST >5x ULN
- PLT<50,000

#### Median Laboratory Values:
- CRP 136 mcg/ml (79-208), D-Dimer 910 ng/ml, Ferritin 929 ng/ml, Lactate 1.4, Creatine 0.9

#### Primary outcome: Mechanical ventilation or death by day 28
- Cumulative percentage of patients who had received mechanical ventilation or who had died by day 28 was significantly lower in the tocilizumab group (12.0%; [95% CI: 8.5-16.9]) than in the placebo group (19.3%; [95% CI: 13.3-27.4]) (HR 0.56; [95% CI: 0.33-0.97]; p=0.04)

#### Secondary outcome:
- No significant improvement in Time to Improvement in Clinical Status (HR 1.16; [95% CI: 0.92-1.42])
- No significant difference in Time to Hospital Discharge or Readiness (HR; 1.16; [95% CI: 0.91-1.48])
- Median Time to Clinical Failure could not be estimated in either group (HR 0.55; [95% CI: 0.33-0.93])
- Mortality by day 28: Tocilizumab 10.4% [95% CI: 7.2-14.9] and Placebo 8.6% [95% CI: 4.9-14.7]; Weighted difference 2.0 percentage points (-5.2-7.8)

#### Adverse events:
- Event related to tocilizumab (n=32 (12.8%)) or placebo (n=5, 3.9%) as determined by investigator
- Serious: Tocilizumab (n=38, 15.2%); Placebo (n=25, 19.7%)
- Incidence of Grade 3 or 5 events and infection were similar between groups.
- None leading to withdrawal of the trial or leading to dose modification/interruption

#### Median Laboratory Values:
- CRP 136 mg/L, D-Dimer 1.5 mcg/ml, Ferritin 1395.39

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**Conclusions**

The likelihood of progression to mechanical ventilation or death by day 28 was significantly lower among patients who received tocilizumab plus standard care. No overall mortality benefit was observed.

**Limitations:**
- A slightly higher number of patients in the placebo group received steroids compared to the tocilizumab group which may impact mortality outcomes.
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<td>Veiga, January 2020 (TOCIBRAS) LOE 1b, n=129</td>
<td>Randomized, open-label, parallel, superiority trial of 129 severe or critically ill hospitalized patients with COVID-19 who were symptomatic for ≥3 days across 9 Brazilian hospitals. <strong>Randomized to tocilizumab (n=65; 8 mg/kg, max 800 mg) or usual care (n=62, n=2 tocilizumab)</strong>. Included: - Hospitalized adults ≥18 years with confirmed COVID-19 AND evidence of pulmonary infiltrates on CT or X-Ray AND - Receiving oxygen supplementation to maintain O2SAT &gt;93% OR mechanical ventilation for less than 24 hours AND - Evidence of abnormal levels of at least 2 biomarkers (D-Dimer &gt; 2.74 nmol/L, CRP ≥50 mg/L, ferritin &gt;300 mcg/L, or lactate &gt;ULN) Exclusion: - Active uncontrolled infection - Elevated AST or ALT &gt;5xULN - GFR &lt;30 ml/min/1.73 m² Patient selection: - Mean age 57 (SD 14), male (68%), concomitant corticosteroids (7%) - More patients in the tocilizumab group were using supplementary oxygen at enrollment (60% vs 44%), whereas use of non-invasive ventilation or high flow oxygen through a nasal cannula was higher in the control group (23% vs 41%); mechanical ventilation (17% vs 16%) - Ordinal Scale Clinical Status 4 (60% vs 44%), 5 (23% vs 41%), 6 (17% vs 16%)</td>
<td><strong>Primary outcome:</strong> - No significant difference in 28-day mortality or in-hospital mortality were observed (OR 2.70; [95%CI: 0.97-8.35]) - Clinical status at day 8 and day 29 were also not different between groups - No significant differences were found in other secondary outcomes, including ventilator-free days within 29 days, time to independence from supplemental oxygen within 29 days, secondary infections, and thromboembolic events.</td>
<td><strong>Limitations:</strong> - Open-label design - Small sample size - Not powered to detect treatment effect - Median time to symptom onset not discussed - Respiratory support at baseline differed significantly between groups - Patients in control group tended to be sicker - Low use of corticosteroids</td>
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<td>Stone, October 2020 (BACC) LOE 1b, n=243</td>
<td>Randomized, double-blind, placebo-controlled, trial of 243 NON-ICU patients hospitalized with COVID-19 across 7 Boston area hospitals. <strong>Randomized to tocilizumab (n=161; 8 mg/kg, max 800 mg) or placebo (n=82).</strong> Included: - Hospitalized adults 19-85 years with confirmed COVID AND at least two of the following: - Fever within 72 hours (38°C), pulmonary infiltrates, need for supplemental oxygen to maintain O2 SAT &gt;92% AND at least one of the following laboratory criteria: - CRP &gt;50 mg/L, ferritin &gt;500 ng/ml, D-Dimer &gt;1000 ng/ml, lactate &gt;250 U/L Exclusion: - Receiving oxygen supplementation &gt;10 L/minute</td>
<td><strong>Tertiary and Exploratory outcomes:</strong> - Admission to ICU or death (0.97; [95%CI: 0.50-1.88]) - No difference in duration of supplemental oxygen or mechanical ventilation <strong>Primary outcome:</strong> - Use of tocilizumab was not associated with an improvement in mechanical ventilation or death at 15 days (1.54; [95% CI: 0.66-3.66], p=0.32) - Death at 15 days was higher for those treated with tocilizumab (OR 6.42; [95% CI: 1.59-43.2]) <strong>Secondary outcome:</strong> - No significant difference in 28-day mortality or in-hospital mortality were observed (OR 2.70; [95%CI: 0.97-8.35]) - Clinical status at day 8 and day 29 were also not different between groups - No significant differences were found in other secondary outcomes, including ventilator-free days within 29 days, time to independence from supplemental oxygen within 29 days, secondary infections, and thromboembolic events. <strong>Post-hoc analysis:</strong> - Shorter hospital stay was observed in tocilizumab treated patients (0.75; [95%CI: 0.58-0.94]) - No significant effect of respiratory support at baseline on primary outcome was noted between groups <strong>Adverse events:</strong> - Tocilizumab had numerically higher adverse events compared to standard of care alone (43% vs 34%) but was not statistically significant (p=0.26)</td>
<td><strong>Tocilizumab was not superior to standard of care alone and may be associated with higher mortality in patients with severe or critical COVID-19</strong> <strong>Limitations:</strong> - Median time to symptom onset not discussed - Respiratory support at baseline differed significantly between groups - Patients in control group tended to be sicker - Low use of corticosteroids - Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with elevated inflammatory markers and confirmed COVID-19 - Findings may be skewed by lack of clarity of use in time course of disease</td>
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<td>Hermine, October 2020 (CORIMUNO-TOCI-1 and CORIMUNO-19) LOE 1b, n=130</td>
<td><strong>Study Design</strong>: Multi-center, investigator-initiated, open-label, bayesian randomized clinical trial of 130 patients hospitalized among 9 French hospitals with moderate-to-severe COVID-19 pneumonia requiring at least 3L/min of oxygen but without mechanical ventilation or ICU admission. Randomized to tocilizumab (n= 64; 8 mg/kg, max 600 mg) on Day 1 and 400 mg on Day 3 if oxygen requirement not decreased by 50% at discretion of physician (n=67). Included: <strong>CORIMUNO-19 cohort</strong> included hospitalized adults ≥ 18 years with confirmed COVID with moderate-severe-or critical pneumonia (WHO CPS score 5 requiring &gt; 3 L/min) <strong>CORIMUNO-TOCI-1 cohort</strong> included moderate patients with WHO CPS score of 5 requiring &gt; 3 L/min but without noninvasive ventilation or mechanical ventilation.</td>
<td><strong>Primary outcome</strong>:  - No reduction in WHO CPS scores during follow-up at day 4 (0.57; [95%CI: 0.24-1.32])  - No difference in cumulative incidence of noninvasive ventilation, high-flow oxygen, mechanical ventilation or death at Day 14 (RR 0.18; [95% CI: 0.4-31])  - No difference in numerical value of patients with mechanical ventilation or death at Day 14 (0.58; [90% CI: 0.30-1.09])</td>
<td>Some patients received remdesivir and non-dexamethasone glucocorticoids. 18 patients in the tocilizumab group and 5 in the placebo group received steroids.</td>
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<td>Hermine, October 2020 (CORIMUNO-TOCI-1 and CORIMUNO-19) LOE 1b, n=130</td>
<td><strong>Exclusion</strong>: Uncontrolled bacterial, fungal, or non-COVID viral infection  - Active TB or LTBI with &lt; 1 month of treatment  - Any prior investigational immunologic therapy (e.g. biologic or JAK inhibitor) within 28-days or 3 half-lives of the agent  - Receipt of tocilizumab for the treatment of other conditions within 30 days  - History of hypersensitivity to tocilizumab  - Any concurrent immunosuppressive medication that the PI believes would put the patient at higher risk  - Oral or IV corticosteroid for non-COVID-19 indication within the last 7 days at a dose of ≥ 10 mg equivalent prednisone  - History of diverticulitis or bowel perforation  - ANC &lt;500, Platelets &lt;50,000, AST/ALT &gt; 5X ULN  - Treatment with convalescent plasma</td>
<td><strong>Secondary outcome</strong>:  - No difference in WHO CPS scores during follow-up at day 4 (0.60; [95% CI: 0.27-1.28]), Day 7 (0.86 [95% CI: 0.43-1.7]), Day 14 (0.76; [95% CI: 0.40-1.42]), and longitudinal analysis (0.44; [95% CI: 0.14-1.36]).  - No difference in incidence of oxygen supply independency or Discharge at Day 28  - No difference in mortality at Day 14 (1.19; [95% CI: 0.40-3.55]), Day 14 (0.92; [95% CI: 0.33-2.53]), or Overall Survival</td>
<td>Tocilizumab was not effective in improving clinical outcomes or survival in patients with COVID-19 pneumonia requiring oxygen support but not admitted to the ICU.</td>
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<td>Hermine, October 2020 (CORIMUNO-TOCI-1 and CORIMUNO-19) LOE 1b, n=130</td>
<td><strong>Adverse events</strong>:  - Serious adverse events were similar among groups (p=0.21)</td>
<td>Limitations:  - Open-label, unblinded study  - Small sample size  - Change in protocol modifying inclusion criteria and late primary outcome  - Variation in usual care across study sites  - Analysis of patients w/ moderate or severe disease not performed  - Median time from symptom onset to randomization not described</td>
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<td>LOE 1b, n=452</td>
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<td>Higher number of patients received antiviral (11% vs 24%) and glucocorticoids (33% vs 61%) in the usual care group</td>
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<td>Results may not be generalizable to all patients (WHO CPS exactly 5 requiring at least 3L/min O2)</td>
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<td>Salvarani, October 2020 (RCT-TCZ-COVID-19)</td>
<td>Prospective, multi-center, open-label, randomized, Phase 2 clinical trial of 126 patients hospitalized among 24 Italian hospitals with COVID-19 and evidence or respiratory failure NOT requiring invasive or semi-invasive mechanical ventilation</td>
<td>Randomized to tocilizumab (n= 60; 8 mg/kg, max 800 mg) within 8 hours of randomization, followed by a second dose after 12 hours or max 800 mg) or placebo (n=144)</td>
<td>Tocilizumab was not effective in improving clinical outcomes or survival in patients with COVID-19 pneumonia NOT requiring semi-invasive or invasive oxygen support or ICU admission</td>
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<td>Limitations:</td>
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<td>Open-label, unblinded study</td>
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<td>Small sample size</td>
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<td>14 patients received tocilizumab after they reached the primary endpoint, which may impact secondary outcomes</td>
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<td>Median time from symptom onset to randomization not described</td>
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<td>There was a significant reduction in incidence of clinical failure among patients not on mechanical ventilation, ICU stay among patients not in the ICU at baseline, and hospital stay but was not significant since the primary endpoint was not met</td>
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<td>Higher number of patients received antiviral (11% vs 24%) and glucocorticoids (33% vs 61%) in the usual care group</td>
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<td>Results may not be generalizable to all patients (WHO CPS exactly 5 requiring at least 3L/min O2)</td>
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<td>Rosas, September 2020 (COVACTA)</td>
<td>Global, multi-center, randomized, double-blind, placebo-controlled, Phase 3 clinical trial of 452 hospitalized patients with severe COVID-19 pneumonia</td>
<td>Randomized to tocilizumab (n= 294; 8 mg/kg, max 800 mg) or placebo (n=144)</td>
<td>Tocilizumab was not effective in improving clinical outcomes or mortality in patients with severe COVID-19 pneumonia</td>
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<tr>
<td>LOE 1b, n=452</td>
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<td>There was a significant reduction in incidence of clinical failure among patients not on mechanical ventilation, ICU stay among patients not in the ICU at baseline, and hospital stay but was not significant since the primary endpoint was not met</td>
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<td>Results may not be generalizable to all patients (WHO CPS exactly 5 requiring at least 3L/min O2)</td>
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</table>

- **Known hypersensitivity to TCZ, pregnancy, current documented bacterial infection, ANC < 1000, PLT < 50**
- **Exclusion evidence or respiratory failure NOT requiring ICU (e.g. DNI)**
- **Included Adults ≥ 18 years**
- **PaO2/FiO2 ratio 200-300 mmHg**
- **Fever greater than 38C for last 2 days and/or CRP ≥ 10 mg/dL or increased 2x baseline at admission**
- **Exclusion ARDS w/ PaO2/FiO2 < 200 mmHg or requiring non-invasive or invasive ventilation or presence of shock or concomitant organ failure that require ICU admission**
- **Known hypersensitivity to tocilizumab**
- **Pregnancy**
- **Any condition preventing future admission to ICU (e.g. DNI)**
- **Treatment with immunosuppressants or anti-rejection therapy**
- **Known active infection or other clinical conditions that contradict use**
- **GPT or GOT > 5x ULN, ANC < 500, PLT < 50**
- **Diverticulitis or intestinal perforation**
- **Suspicion or latent tuberculosis**

**Primary outcome:**
- No difference in clinical worsening within 14 days following randomization (1.05; [95% CI: 0.59-1.86], p=0.87)

**Secondary outcome:**
- No difference in ICU admission within 14 days following randomization (1.26; [95% CI: 0.43-3.91])
- No difference in Day 14 or 30-day Mortality (1.05; [95% CI: 0.07-16.4]) and 2.10; [95% CI: 0.20-22.6], respectively)
- No difference in Hospital Discharge rates at Day 14 and Day 30 ((0.99; [95% CI: 0.73-1.35]) and 0.98; [95% CI: 0.87-1.09], respectively)

**Adverse events:**
- No difference in adverse events between groups

**Median Laboratory Values**
- CRP 6.5 mg/dL, D-Dimer 0.455 mcg/ml, Ferritin 533.5 ng/ml, IL-6 34.3 pg/ml

**Results**
- Median time to hospital discharge was 8 days shorter with tocilizumab
- No difference in 28-day Mortality (1.19; [95% CI: 0.81-1.76], p=0.87)
- No difference in day 28 Clinical Worsening (1.05; [95% CI: 0.59-1.86], p=0.87)
- No difference in ICU Admission within 14 days following randomization (1.26; [95% CI: 0.43-3.91])
- No difference in 28-day Mortality (1.05; [95% CI: 0.07-16.4]) and 2.10; [95% CI: 0.20-22.6], respectively)
- No difference in Hospital Discharge rates at Day 14 and Day 30 ((0.99; [95% CI: 0.73-1.35]) and 0.98; [95% CI: 0.87-1.09], respectively)
- No difference in duration or ICU stay (p=0.14), ventilator free days by day 28 (p=0.22), respectively)
- No difference in 28-day Mortality (1.19; [95% CI: 0.81-1.76], p=0.87)
- No difference in clinical status on 7-day Mortality (1.41; [95% CI: 0.99-2.05])
- No difference in 28-day mortality (p=0.94)
- Median time to hospital discharge was 8 days shorter with tocilizumab (1.35; [95% CI: 1.02-1.79]) but cannot be interpreted as statistically significant
- No difference in time to improvement of ≥ 2 categories on 7-category ordinal scale (1.26; [95% CI: 0.97-1.64])
- No difference in duration or ICU stay (p=0.14), ventilator free days by day 28 (p=0.03), incidence of mechanical ventilation (p=0.14)

**Limitations:**
- Open-label, unblinded study
- Small sample size
- 14 patients received tocilizumab after they reached the primary endpoint, which may impact secondary outcomes
- Median time from symptom onset to randomization not described

**Conclusion**
- Tocilizumab was not effective in improving clinical outcomes or mortality in patients with severe COVID-19 pneumonia
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malgie, September 2020&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Systematic review and meta-analysis of 10 observational studies encompassing 1358 patients treated with tocilizumab. Nine studies were of high quality</td>
<td></td>
<td>Tocilizumab was associated with lower mortality (NNT 11). Mortality benefit no longer significant when corticosteroids were used</td>
</tr>
<tr>
<td>LOE 1b, n=1358</td>
<td>Concomitant glucocorticoids (8/10 studies), remdesivir (2/20), hydroxychloroquine (10/10), lopinavir/ritonavir (6/10), azithromycin (6/10), anticoagulation (5/10)</td>
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<tr>
<td>Gupta, October 2020&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Retrospective, multicenter cohort of 3924 patients admitted across 68 US hospitals from March 4 to May 10, 2020</td>
<td></td>
<td>Early tocilizumab was associated with lower mortality in critically ill patients</td>
</tr>
<tr>
<td>LOE 3, n=3924</td>
<td>Patients were randomized within 2 days of ICU admission (TCZ n=433), tended to be younger (median age 58), had higher prevalence of hypoxemia on ICU admission (47.3%), and mechanical ventilation with PaO2/FiO2 &lt; 200 mmHg (37.9%)</td>
<td></td>
<td>Limitations: Retrospective study Treatment groups differed significantly at baseline. Tocilizumab treated patients tended to be younger with fewer comorbidities Data collection did not include the number of administered doses of tocilizumab or other administered agents, such as corticosteroids Results may not be generalizable to all patients Possible unmeasured confounding variables</td>
</tr>
<tr>
<td>Kimmig, October 2020&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Retrospective study of 111 critically ill COVID-19 patients at a single center in Chicago of whom 54 patients received tocilizumab, as per inter-hospital COVID-19 guidance and discretion of primary team</td>
<td></td>
<td>Tocilizumab was associated with increased secondary bacterial infections and higher mortality</td>
</tr>
<tr>
<td>LOE 3, n=111</td>
<td></td>
<td>Median Laboratory Values</td>
<td>Limitations:</td>
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<tr>
<td></td>
<td>CRP 150.3 pmol/ml, Ferritin 2.2 pmol/ml, IL-6 71.2 pg/ml</td>
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<td>Primary outcome:</td>
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<td>Tocilizumab associated with lower mortality (RR 0.27; [95% CI: 0.12-0.59], I^2=61%). After adjusting for outlier, significance was maintained (0.34; [95% CI: 0.18-0.66], I^2=19%)</td>
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<td>Tocilizumab treatment effect of TCZ on mortality was smaller compared with studies that did not use glucocorticoids (I^2 = 33%). In a subgroup analysis, there was no longer a difference in mortality when glucocorticoids without lopinavir was used</td>
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<td>Secondary outcome:</td>
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<td>No differences in mechanical ventilation, mortality after mechanical ventilation, or ICU admission observed</td>
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<td>Adverse events:</td>
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<td></td>
<td>No difference in secondary infection, neutropenia, or liver impairment</td>
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<td>Limitations:</td>
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<td>Possible unmeasured confounding variables</td>
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**Study Design:**
- Use of investigational treatments (except antivirals) and immunomodulatory therapy. Low dose steroids allowed
- Concomitant glucocorticoids (8/10 studies), remdesivir (2/20), hydroxychloroquine (10/10), lopinavir/ritonavir (6/10), azithromycin (6/10), anticoagulation (5/10)
- Adults ≥ 18 years with laboratory-confirmed COVID
- Enrolled in a placebo-controlled trial involving tocilizumab or other IL-6 antagonists
- Hospitalization for 1 week or more before ICU admission
- AST or ALT > 5x ULN
- Receipt of tocilizumab or IL-6 antagonist during first 2 days of ICU admission
- Receipt of tocilizumab before ICU admission
- CRP 150.3 pmol/ml, Ferritin 2.2 pmol/ml, IL-6 71.2 pg/ml
- Tocilizumab associated with higher risk of secondary bacterial infections including hospital acquired pneumonia and ventilator associated pneumonia compared to non-treated patients (p=0.021)
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
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<tbody>
<tr>
<td>Biran, August 2020</td>
<td>Retrospective, propensity-matched study of 764 hospitalized COVID-19 ICU patients across 13 NJ hospitals between March 1 and April 22, 2020 of whom 210 (27%) received tocilizumab per hospital guidance and discretion of primary team. Protocol recommended standard dose of 400 mg with the ability to receive a second dose if worsening oxygenation before mechanical ventilation: 400 mg (n=206, 98%), 8 mg/kg (n=2). Other doses (n=2), (n=25, 12% received two infusions) Tocilizumab was administered a median of 9 days (IQR 6–12) after the start of patient–reported symptoms, a median of 3 days (1–7) from the date of hospitalization, and a median of 0 days (0–2) from the date of ICU support. Included Adults ≥ 18 years with laboratory-confirmed COVID who needed support in the ICU Exclusion Pregnancy, enrollment in clinical trial, patients receiving tocilizumab for chronic rheumatologic conditions.</td>
<td>Secondary outcome: Tocilizumab use was independently associated with the development of bacterial infections (2.76; [95% CI: 1.11-7.20], p=0.0295) as was APACHE II score (p=0.016) Diagnosis of infection was made approximately 5 days after the administration of tocilizumab (4.9±3.0 days [95% CI: 3.67-6.17]) Higher mortality was observed in patients treated with tocilizumab (35.2% vs 19.3%, p=0.020)</td>
<td>Tocilizumab was associated with lower mortality in critically ill patients, especially those who required mechanical ventilation and those younger than 65. Limitations: Retrospective study, although propensity-matched cohort, possibility of confounding exists. Tocilizumab was given late during course of disease (median 9 days) but within 24 hours of ICU admission. Protocol deviation occurred in respect to dosing in some patients.</td>
</tr>
<tr>
<td>Albertini, September 2020</td>
<td>Single-center observational study of 44 patients hospitalized with COVID-19 of whom 22 patients were treated with tocilizumab and were compared with 22 patients not treated with tocilizumab. Tocilizumab was prescribed at a fixed dose of 600 mg for patients &lt;100 kg and 800 mg for those &gt;100 kg. 2 doses (n=20. 90.9%) On average, patients received the first injection of TCZ 10 days after the onset of symptoms (range 3–21 days).</td>
<td>Key Findings: The average respiratory rate was lower in the tocilizumab treated group at day 14 (21.5 vs. 25.5 breaths/min at day 14, [95% CI: -7.5–0.4]; p=0.03). The average duration for oxygen withdrawal was 10.8 days for the TCZ group and 6.4 days for the control group (p=0.003) A significant reduction in CRP was noted at Day 7 after TCZ (6.5 mg/L vs. 56.5 mg/L, p=0.04) A trend towards decreased invasive mechanical ventilation requirement was noted but was not statistically significant (2/22 vs. 6/22, [95% CI: -0.4-0.1]; p=0.12)</td>
<td>Tocilizumab was associated with decreased respiratory rates at day 14 and decreased CRP levels by day 7. Oxygen withdrawal was faster for those not treated with tocilizumab. No difference in invasive mechanical ventilation requirements were observed. Limitations: Retrospective study.</td>
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<tr>
<td>Guaraldi, August 2020</td>
<td>Retrospective, multicenter, observational study of 544 patients</td>
<td>Primary outcome:</td>
<td>Tocilizumab was associated with reduction in risk of invasive mechanical ventilation or death at the cost of increased risk of new infection</td>
</tr>
<tr>
<td>LOE 3, n=544</td>
<td>with severe COVID-19 pneumonia admitted to tertiary care centers</td>
<td>– Patients who received tocilizumab showed a significant reduction in risk of invasive mechanical ventilation or death when compared with those receiving standard of care only (HR 0.60; [95% CI: 0.43–0.84]; p=0.0030)</td>
<td>Tocilizumab was associated with reduction in risk of invasive mechanical ventilation or death at the cost of increased risk of new infection</td>
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<td>across Italy treated with tocilizumab in addition to standard of</td>
<td>– After controlling for the key identified confounders of sex, age, SOFA score, recruiting center, and duration of symptoms, the treatment effect was even larger (p=0.020)</td>
<td>Treatment effect was largest for those with PaO2/FiO2 &lt; 150 mmHg</td>
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<td>care (n=179) and compared to those who didn’t receive the drug</td>
<td>– For the composite endpoint, we found no evidence for a difference between subcutaneous and intravenous tocilizumab (p=0.64)</td>
<td>Limitations: Retrospective, open-label</td>
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<td>(n=365)</td>
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<td>SOFA and PaO2/FiO2 ratios at baseline differed significantly across patients</td>
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<td>TCZ was given 8 mg/kg (max 800 mg) in two infusions doses 12</td>
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<td>Patients who received standard of care tended to be older</td>
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<td>hours apart or subcutaneously at 162 mg in two simultaneous</td>
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<td>doses (324 mg total)</td>
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<td>– Adults ≥ 18 years with laboratory-confirmed COVID and severe</td>
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<td>pneumonia defined as at least one of the following:</td>
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<td>– RR ≥ 30 BPM, O2SAT &lt; 93% on RA, PaO2/FiO2 &lt; 300 mgHg, lung</td>
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<td>– Exclusion</td>
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<td>– Coexistent infection</td>
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<td>– PaO2/FiO2 &gt; 300 mmHg</td>
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<td>– Chronic or current glucocorticoid use</td>
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<td>– History of severe allergic reaction to monoclonal antibodies</td>
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<td>– ANC &lt; 500</td>
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<td></td>
<td>– Acute diverticulitis, IBD or other symptomatic GI disease</td>
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<td>– Severe hematological, renal, or liver impairment</td>
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<td>Mean age 65 years, male 70.5%</td>
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<td>Adverse events:</td>
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<td>– Incidence of adverse events including bacteremia and secondary</td>
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<td>bacterial infections were similar between groups but there was</td>
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<td>an increased incidence of new infections diagnosed in the</td>
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<td>tocilizumab group (p&lt;0.0001)</td>
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<td>Somers, July 2020</td>
<td>Retrospective, single-center, controlled study of 154 patients</td>
<td>Primary outcome:</td>
<td>Tocilizumab was associated with increased survival inpatients requiring mechanical ventilation at the cost of increased risk of superinfection</td>
</tr>
<tr>
<td>LOE 3, n=154</td>
<td>admitted to a Michigan hospital with COVID-19 requiring</td>
<td>– Survival probability was significantly higher among tocilizumab-treated</td>
<td>Limitations: Retrospective study</td>
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<td>mechanical ventilation of whom 78 patients were treated with</td>
<td>compared with untreated patients (p=0.0189)</td>
<td>Tocilizumab was given at discretion of physician (risk for selection bias)</td>
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<td>tocilizumab and 76 were not</td>
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<td>TCZ was given 8 mg/kg (Max 800 mg) at discretion of physician.</td>
<td>Secondary outcome:</td>
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<td>Additional doses were discouraged: (47% treated within 24 hours</td>
<td>– Inverse probability of treatment weights (IPTW)-adjusted models,</td>
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<td>of intubation; 26% &gt;48 hours of intubation)</td>
<td>tocilizumab was associated with a 45% reduction in hazard of death (HR 0.55; [95% CI: 0.33-0.90])</td>
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<td>Excluded</td>
<td>– Tocilizumab was associated with improvement on a six-point ordinal</td>
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<td>scale that incorporated mechanical ventilation, development of superinfection and discharge from the hospital (OR 0.6; p ≤ 0.03 for IPTW-weighted models)</td>
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<tr>
<td>Study</td>
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<tr>
<td>Price, June 2020(^1)</td>
<td>Retrospective, single-center, consecutive study of 239 hospitalized adults ≥ 18 years in Connecticut hospital with COVID-19 of whom 153 received tocilizumab: 44% had non-severe disease with evolving CRS while others had severe disease (i.e. receiving ≥ 3 L of supplemental oxygen to maintain O2SAT &gt; 93% or mechanical ventilation)</td>
<td>Tocilizumab patients were twice as likely to develop superinfections (54% vs 26%; p&lt;0.001), but there was no difference in 28-day case fatality rate among tocilizumab-treated patients with versus without superinfection (22% vs 15%; p=0.42). Staphylococcus aureus accounted for ~50% of bacterial pneumonia</td>
<td>Tocilizumab treated patients were younger and less likely to have comorbidities. Lower D-dimer and higher albumin levels were also observed. Patients treated with tocilizumab also received other agents.</td>
</tr>
</tbody>
</table>
| Capra, June 2020\(^2\)       | Retrospective consecutive study of 85 patients admitted to an Italian hospital with COVID-19-related respiratory failure not requiring mechanical ventilation of whom 62 received tocilizumab | **Key Findings:**  
- Overall 14-day survival was 87% and was lower for patients with severe disease (78% vs 93%, p<0.001). It was also lower for white vs hispanic/latino population which was not consistent with previous studies  
- Survival for tocilizumab-treated patients with severe and nonsevere disease did not differ (83% vs 91%; p=0.10)  
- Throughout the 14 days following tocilizumab administration, the proportion whose oxygenation levels improved or remained the same initially declined but more so in patients with severe disease, followed by steady improvements in both groups  
- Patients with severe disease were more likely to have higher admission CRP and IL-6 levels, abnormal chest radiographs, and to receive adjuvant medications such as hydroxychloroquine, glucocorticoids, and tocilizumab | **Limitations:**  
- No difference in survival was demonstrated for patients with severe or non-severe disease  
- Retrospective study  
- Tocilizumab was given via algorithm in patients with severe disease initially, then opened to non-severe adults mid-study  
- Other medications that can influence results were not assessed  

<table>
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<tr>
<td></td>
<td><strong>Inclusion</strong></td>
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</table>
- Within 4 days of hospital admission  
- RR ≥ 30 BPM, O2SAT < 93% on RA, PaO2/FiO2 < 300 mmHg  
The median interval time between symptom onset and hospitalization was 7 days (IQR, 5 to 10 days) | **Primary outcome:**  
- Patients receiving tocilizumab showed significantly greater survival rate as compared to control patients (p=0.004)  
**Secondary outcome:**  
- Complete recovery was seen in 92% of tocilizumab treated patients and were discharged after a mean 12.5 days (while 8% died), whereas only 42.1% of the control patients completely recovered  
- Respiratory function improved in 64.8% of the observations in tocilizumab patients who were still hospitalized, whereas 100% of controls worsened and needed mechanical ventilation  
**Adverse events:**  
- No side effects were reported. Intestinal perforations or bacterial infections were not observed | Tocilizumab treated patients experienced improved survival, respiratory function, and complete recovery.  
**Limitations:**  
- Retrospective study  
- Small sample size  
- Patients treated with tocilizumab tended to be younger with less comorbidities  
- No information is given as to how patients were selected to receive tocilizumab; selection bias possible. |

References:
2. Veiga VC. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ. 2021;372:n84. doi: https://doi.org/10.1136/bmj.n84


