Table 4e. Interleukin-6 Inhibitors: Selected Clinical Data

Last Updated May 31, 2022

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for IL-6 inhibitors. The studies summarized below are those that have had the greatest impact on the Panel’s recommendations. This table may include data from preprints or articles that have not been peer reviewed. This table will be updated as new information becomes available.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Results</th>
<th>Limitations and Interpretation</th>
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<tr>
<td><strong>RECOVERY</strong>: Open-Label RCT of Tocilizumab and Usual Care in Hospitalized Adults With COVID-19 in the United Kingdom[^1]</td>
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<tr>
<td><strong>Key Inclusion Criteria:</strong></td>
<td><strong>Participant Characteristics:</strong></td>
<td><strong>Key Limitations:</strong></td>
</tr>
<tr>
<td>• Evidence of COVID-19 progression ≤21 days after initial randomization to an intervention within the RECOVERY protocol, defined as:</td>
<td>• Mean age 64 years; 67% men; 76% White</td>
<td>• Arbitrary CRP ≥75 mg/L cutoff for enrollment</td>
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<tr>
<td>• SpO₂ &lt;92% on room air or receipt of supplemental oxygen; <em>and</em></td>
<td>• 95% with PCR-confirmed SARS-CoV-2 infection</td>
<td>• Difficult to define exact subset of patients in RECOVERY cohort who were subsequently selected for secondary randomization/tocilizumab trial</td>
</tr>
<tr>
<td>• CRP ≥75 mg/L</td>
<td>• At baseline:</td>
<td><strong>Interpretation:</strong></td>
</tr>
<tr>
<td><strong>Key Exclusion Criterion:</strong></td>
<td>• 45% on conventional oxygen</td>
<td>• Among hospitalized COVID-19 patients with hypoxemia and elevated CRP, tocilizumab was associated with reduced all-cause mortality and shorter time to discharge alive.</td>
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<tr>
<td>• Non-SARS-CoV-2 infection</td>
<td>• 41% on HFNC oxygen or NIV</td>
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<tr>
<td><strong>Interventions:</strong></td>
<td>• 14% on MV</td>
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<tr>
<td>• Single weight-based dose of tocilizumab (maximum 800 mg) and possible second dose (n = 2,022)</td>
<td>• 82% on corticosteroids</td>
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<td>• Usual care (n = 2,094)</td>
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<tr>
<td><strong>Primary Endpoint:</strong></td>
<td><strong>Primary Outcomes:</strong></td>
<td></td>
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<tr>
<td>• 28-day all-cause mortality</td>
<td>• 28-day all-cause mortality: 31% in tocilizumab arm vs. 35% in usual care arm (rate ratio 0.85; 95% CI, 0.76–0.94; <em>P</em> = 0.003)</td>
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<tr>
<td><strong>Key Secondary Endpoints:</strong></td>
<td>• 28-day all-cause mortality among those who required MV at baseline: 49% in tocilizumab arm vs. 51% in usual care arm (risk ratio 0.93; 95% CI, 0.74–1.18)</td>
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<tr>
<td>• Time to discharge from hospital, alive, within 28 days</td>
<td><strong>Secondary Outcomes:</strong></td>
<td></td>
</tr>
<tr>
<td>• Among those not on MV at enrollment, death or receipt of MV within 28 days</td>
<td>• Proportion discharged alive from hospital within 28 days: 57% in tocilizumab arm vs. 50% in usual care arm (rate ratio 1.22; 95% CI, 1.12–1.33; <em>P</em> &lt; 0.0001)</td>
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<tr>
<td></td>
<td>• Median time to discharge: 19 days in tocilizumab arm vs. 28 days in usual care arm</td>
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<td></td>
<td>• Proportion not on MV at baseline who died or required MV within 28 days: 35% in tocilizumab arm vs. 42% in usual care arm (rate ratio 0.84; 95% CI, 0.77–0.92; <em>P</em> &lt; 0.0001)</td>
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</table>

[^1]: [Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/21/2022](https://www.covid19treatmentguidelines.nih.gov/)
REMAP-CAP: Open-Label, Adaptive-Platform RCT of Tocilizumab and Sarilumab in Adults With COVID-19 in 21 Countries in Europe and North America

**Methods**

**Key Inclusion Criteria:**
- ICU admission
- Suspected or laboratory-confirmed COVID-19
- Receipt of MV, NIV, or cardiovascular support

**Key Exclusion Criteria:**
- >24 hours after ICU admission
- Presumption of imminent death
- Immunosuppression
- ALT >5 times ULN

**Interventions:**
- SOC plus 1 of the following (drug selection based on provider preference, availability, or adaptive probability):
  - Single dose tocilizumab 8 mg/kg IV and possible second dose in 12–24 hours (n = 952)
  - Single dose sarilumab 400 mg IV (n = 485)
- SOC alone (n = 406)

**Participant Characteristics:**
- Mean age 60 years; 69% men; 75% White
- 86% PCR-confirmed SARS-CoV-2 infection
- Median 14 hours from ICU admission to enrollment
- At baseline:
  - 68% on HFNC oxygen or NIV
  - 32% on MV
  - On corticosteroids: 67% in SOC arm, 82% in tocilizumab arm, 89% in sarilumab arm

**Primary Outcomes**

**Tocilizumab vs. SOC:**
- Median organ support-free days: 7 in tocilizumab arm vs. 0 in SOC arm
- Improved composite outcome, by ordinal scale: median aOR 1.46 (95% CrI, 1.13–1.87)
- Highest CRP tercile: aOR 1.87 (95% CrI, 1.35–2.59)
- Outcomes consistent across subgroups according to oxygen requirement at baseline

**Sarilumab vs. SOC:**
- Median organ support-free days: 9 in sarilumab arm vs. 0 in SOC arm
- Improved composite outcome, by ordinal scale: median aOR 1.50 (95% CrI, 1.13–2.00)
- Highest CRP tercile: aOR 1.85 (95% CrI, 1.24–2.69)
- Outcomes consistent across subgroups according to oxygen requirements at study entry

**Secondary Outcomes**

**Tocilizumab vs. SOC:**
- In-hospital survival: 66% in tocilizumab arm vs. 63% in SOC arm (aOR 1.42; 95% CrI, 1.05–1.93)

**Sarilumab vs. SOC:**
- In-hospital survival: 67% in sarilumab arm vs. 63% in SOC arm (aOR 1.51; 95% CrI, 1.06–2.20)

**Results**

**Key Limitation:**
- The SOC arm closed in November 2020, after which patients were randomized to active arms only; enrollment in the tocilizumab and sarilumab arms was partially nonconcurrent with the SOC arm, and although comparisons to the SOC arm were adjusted for time period, there is a possibility of bias.

**Interpretation:**
- Among patients with respiratory failure who were within 24 hours of ICU admission, the tocilizumab and sarilumab arms had higher rates of in-hospital survival and shorter durations of organ support than the SOC arm.
- These results were reported in a preprint and are consistent with those for a smaller cohort previously published in a peer-reviewed article.
- The treatment effect appeared to be strongest in the highest CRP tercile.
- Tocilizumab and sarilumab were similarly effective, with a 99% probability of noninferiority of sarilumab.
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<tr>
<th>Methods</th>
<th>Results</th>
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<tr>
<td><strong>COVACTA</strong>: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in 9 Countries in Europe and North America(^4)</td>
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<tr>
<td><strong>Key Inclusion Criteria:</strong></td>
<td><strong>Participant Characteristics:</strong></td>
<td><strong>Key Limitations:</strong></td>
</tr>
<tr>
<td>• PCR-confirmed SARS-CoV-2 infection</td>
<td>• Mean age 61 years; 70% men; 58% White</td>
<td>• Modest power to detect differences in Day 28 clinical status</td>
</tr>
<tr>
<td>• Hypoxemia</td>
<td>• Hypoxemia</td>
<td>• More patients in placebo arm than tocilizumab arm received corticosteroids.</td>
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<tr>
<td>• Bilateral chest infiltrates</td>
<td>• 30% on HFNC oxygen or NIV</td>
<td><strong>Interpretation:</strong></td>
</tr>
<tr>
<td><strong>Key Exclusion Criteria:</strong></td>
<td>• 38% on MV</td>
<td>• There was no difference in Day 28 clinical status or survival between the tocilizumab and placebo recipients.</td>
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<tr>
<td>• Presumption of imminent death</td>
<td>• 25% with multiorgan failure</td>
<td>• The median time to discharge was significantly shorter in the tocilizumab arm than in the placebo arm.</td>
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<tr>
<td>• Presence of active non-SARS-CoV-2 infection</td>
<td>• Received corticosteroids at entry or during follow-up: 36% in tocilizumab arm, 55% in placebo arm</td>
<td>• Although the result was not statistically significant, the tocilizumab arm had a shorter ICU LOS than the placebo arm.</td>
</tr>
<tr>
<td><strong>Interventions:</strong></td>
<td><strong>Primary Outcome:</strong></td>
<td></td>
</tr>
<tr>
<td>• Single dose of tocilizumab 8 mg/kg and possible second dose, plus SOC (n = 294)</td>
<td>• Day 28 clinical status: no significant difference between arms ((P = 0.31))</td>
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<tr>
<td>• Placebo plus SOC (n = 144)</td>
<td><strong>Secondary Outcomes:</strong></td>
<td></td>
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<tr>
<td><strong>Primary Endpoint:</strong></td>
<td>• Median time to discharge: 20 days in tocilizumab arm vs. 28 days in placebo arm (HR 1.35; 95% CI, 1.02–1.79)</td>
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<tr>
<td>• Day 28 clinical status (ordinal score)</td>
<td>• Median ICU LOS: 9.8 days in tocilizumab arm vs. 15.5 days in placebo arm (difference 5.8 days, 95% CI, –15.0 to 2.9)</td>
<td></td>
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<tr>
<td><strong>Key Secondary Endpoints:</strong></td>
<td>• Day 28 mortality: 20% in tocilizumab arm vs. 19% in placebo arm ((P = 0.94))</td>
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</tbody>
</table>
## EMPACTA: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in 6 Countries in North America, South America, and Africa

### Key Inclusion Criteria:
- PCR-confirmed SARS-CoV-2 infection
- COVID-19 pneumonia

### Key Exclusion Criteria:
- Presumption of imminent death
- Receiving NIV or MV

### Interventions:
- Single dose of tocilizumab 8 mg/kg plus SOC, possible second dose (n = 249)
- Placebo plus SOC (n = 128)

### Primary Endpoint:
- Progression to MV, ECMO, or death by Day 28

### Key Secondary Endpoints:
- Time to hospital discharge or readiness for discharge (ordinal score)
- All-cause mortality by Day 28

### Participant Characteristics:
- Mean age 56 years; 59% men; 56% Hispanic/Latinx, 15% Black/African American, 13% American Indian/Alaska Native
- 84% with elevated CRP
- Concomitant medications:
  - Corticosteroids: 80% in tocilizumab arm, 88% in placebo arm
  - RDV: 53% in tocilizumab arm, 59% in placebo arm

### Primary Outcome:
- Proportion who progressed to MV, ECMO, or death by Day 28: 12% in tocilizumab arm vs. 19% in placebo arm (HR 0.56; 95% CI, 0.33–0.97; P = 0.04)

### Secondary Outcomes:
- Median time to hospital discharge or readiness for discharge: 6.0 days in tocilizumab arm vs. 7.5 days in placebo arm (HR 1.16; 95% CI, 0.91–1.48)
- All-cause mortality by Day 28: 10.4% in tocilizumab arm vs. 8.6% in placebo arm (95% CI, −5.2 to 7.8)

### Key Limitation:
- Moderate sample size

### Interpretation:
- In patients with COVID-19 pneumonia, tocilizumab reduced the likelihood of progression to MV, ECMO, or death by Day 28 but did not reduce 28-day all-cause mortality.
### Methods

**BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in the United States**

**Key Inclusion Criteria:**
- Laboratory-confirmed SARS-CoV-2 infection
- ≥2 of the following conditions:
  - Fever >38°C
  - Pulmonary infiltrates
  - Need for supplemental oxygen
- ≥1 of the following laboratory criteria:
  - CRP ≥50 mg/L
  - D-dimer >1,000 ng/mL
  - LDH ≥250 U/L
  - Ferritin >500 ng/mL

**Key Exclusion Criteria:**
- Receipt of supplemental oxygen at rate >10 L/min
- Recent use of biologic agents or small-molecule immunosuppressive therapy
- Receipt of immunosuppressive therapy that increased risk for infection

**Interventions:**
- Tocilizumab 8 mg/kg plus usual care (n = 161)
- Placebo plus usual care (n = 81)

**Primary Endpoint:**
- Receipt of MV or death, according to a time to event analysis; data censored at Day 28

**Key Secondary Endpoints:**
- Clinical worsening by Day 28 (ordinal score)
- Discontinuation of supplemental oxygen among patients receiving it at baseline

### Results

**Participant Characteristics:**
- Median age 60 years; 58% men; 45% Hispanic/Latinx, 43% White
- 50% with BMI ≥30; 49% with HTN; 31% with DM
- 80% receiving oxygen ≤6 L/min; 4% receiving HFNC oxygen; 16% receiving no supplemental oxygen
- Concomitant medications:
  - Corticosteroids: 11% in tocilizumab arm, 6% in placebo arm
  - RDV: 33% in tocilizumab arm, 29% in placebo arm

**Primary Outcome:**
- Day 28 MV or death: 11% in tocilizumab arm vs. 12% in placebo arm (HR 0.83; 95% CI, 0.38–1.81; \( P = 0.64 \))

**Secondary Outcomes:**
- Proportion with clinical worsening of disease by Day 28: 19% in tocilizumab arm vs. 17% in placebo arm (HR 1.11; 95% CI, 0.38–2.10; \( P = 0.73 \))
- Median days to discontinuation of oxygen: 5.0 in tocilizumab arm vs. 4.9 in placebo arm (\( P = 0.69 \))

### Limitations and Interpretation

**Key Limitations:**
- Wide confidence intervals due to small sample size and low event rates
- Few patients received RDV or corticosteroids

**Interpretation:**
- There was no benefit of tocilizumab in preventing MV or death, reducing the risk of clinical worsening, or reducing the time to discontinuation of oxygen. This could be due to the low rate of concomitant corticosteroid use among the study participants.
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</table>
| **Double-Blind, RCT of Sarilumab in Hospitalized Adults With Severe or Critical COVID-19 in 11 Countries in Europe, North America, South America, and Asia**

**Key Inclusion Criteria:**
- COVID-19 pneumonia
- Requirement for supplemental oxygen or intensive care

**Key Exclusion Criteria:**
- Low probability of surviving or remaining at study site
- Dysfunction of ≥2 organ systems and need for ECMO or renal replacement therapy

**Interventions:**
- Sarilumab 400 mg IV (n = 173)
- Sarilumab 200 mg IV (n = 159)
- Placebo (n = 84)

**Primary Endpoint:**
- Time to clinical improvement of ≥2 points on a 7-point scale

**Key Secondary Endpoint:**
- Survival at Day 29

**Participant Characteristics:**
- Median age 59 years; 63% men; 77% White, 36% Hispanic/Latinx
- 39% on HFNC oxygen, MV, or NIV
- 42% with BMI ≥30; 43% with HTN; 26% with type 2 DM
- 20% received systemic corticosteroids before receiving intervention; 63% received ≥1 dose of corticosteroids during the study

**Primary Outcomes:**
- Median time to clinical improvement: 10 days in each sarilumab arm, 12 days in placebo arm
  - Sarilumab 200 mg arm vs. placebo arm: HR 1.03; 95% CI, 0.75–1.40; *P* = 0.96
  - Sarilumab 400 mg arm vs. placebo arm: HR 1.14; 95% CI, 0.84–1.54; *P* = 0.34

**Secondary Outcome:**
- Survival at Day 29: 92% in placebo arm; 90% in sarilumab 200 mg arm ( *P* = 0.63 vs. placebo); 92% in sarilumab 400 mg arm ( *P* = 0.85 vs. placebo)

**Key Limitation:**
- Moderate sample size

**Interpretation:**
- Sarilumab showed no mortality benefit or reduction in time to clinical improvement in hospitalized adults with COVID-19.
**Methods**

**REMDACTA:** Double-Blind RCT of Tocilizumab and Remdesivir in Hospitalized Patients With Severe COVID-19 Pneumonia in Brazil, Russia, Spain, and the United States

<table>
<thead>
<tr>
<th>Key Inclusion Criteria:</th>
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<tbody>
<tr>
<td>• Aged ≥12 years</td>
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<tr>
<td>• PCR-confirmed SARS-CoV-2 infection</td>
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<tr>
<td>• Hospitalized with pneumonia confirmed by CXR or CT and requiring supplemental oxygen &gt;6 L/ min</td>
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</tbody>
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<thead>
<tr>
<th>Key Exclusion Criteria:</th>
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<tbody>
<tr>
<td>• eGFR &lt;30 mL/min</td>
</tr>
<tr>
<td>• ALT or AST &gt;5 times ULN</td>
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<tr>
<td>• Presence of non-SARS-CoV-2 infection</td>
</tr>
<tr>
<td>• Treatment with antivirals, CP, CQ, HCQ, JAK inhibitors</td>
</tr>
</tbody>
</table>

**Interventions:**

- Up to 10 days RDV plus:
  - Tocilizumab 8 mg/kg IV, with second dose within 8–24 hours if indicated (n = 434)
  - Placebo (n = 215)

**Primary Endpoint:**

- Time to discharge or ready for discharge through Day 28

**Key Secondary Endpoints:**

- Time to MV or death through Day 28
- Day 14 clinical status (ordinal score)
- Time to death through Day 28

**Participant Characteristics:**

- Mean age 59 years; 40% in tocilizumab arm and 34% in placebo arm aged ≥65 years; 63% men; 67% White
- Respiratory support:
  - NIV or HFNC oxygen: 78% in tocilizumab arm, 83% in placebo arm
  - MV or ECMO: 15% in tocilizumab arm, 11% in placebo arm
- Corticosteroid use:
  - At baseline: 83% in tocilizumab arm, 86% in placebo arm
  - During trial: 88% in each arm

**Primary Outcome:**

- Time to discharge or ready for discharge through Day 28: 14 days in each arm (HR 0.97; 95% CI, 0.78–1.19; P = 0.74)

**Secondary Outcomes:**

- No difference between arms:
  - Proportion who required MV or died by Day 28: 29% in each arm; time to death not evaluable (HR 0.98; 95% CI, 0.72–1.34; P = 0.90)
  - Mean ordinal score for Day 14 clinical status: 2.8 in tocilizumab arm vs. 2.9 in placebo arm (P = 0.72)
  - Death by Day 28: 18% in tocilizumab arm vs. 20% in placebo arm; time to death not evaluable (HR 0.95; 95% CI, 0.65–1.39; P = 0.79)

**Key Limitations:**

- During the trial, primary outcome changed from clinical status on Day 28 to time to discharge or ready for discharge through Day 28
- Imbalances in patient characteristics at baseline between arms
- Possible underrepresentation of patients with rapidly progressive disease

**Interpretation:**

- Compared with placebo plus RDV, tocilizumab plus RDV did not shorten the time to discharge or ready for discharge in patients with severe COVID-19 pneumonia.
- There was no difference in mortality between the arms.

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**Key:** ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; CP = convalescent plasma; CQ = chloroquine; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; LDH = lactate dehydrogenase; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SpO₂ = oxygen saturation; ULN = upper limit of normal
References


