SARS-CoV-2 and COVID-19

Treatment: Tocilizumab

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Tocilizumab (Actemra)
Tocilizumab

- **Medication Class**: Interleukin-6 (IL-6) receptor blocker

- **FDA Approved for**:
  - Cytokine release syndrome
  - Rheumatoid arthritis and other rheumatologic conditions

- **Dose for Cytokine Release Syndrome**
  - Weight $\geq$ 30 kg: 8 mg/kg IV x 1 dose (max 800 mg)
  - Weight $\leq$ 30 kg: 12 mg/kg IV x 1 dose (max 800 mg)

- **Dose for COVID-19**
  - Range of doses used in studies

- **Adverse Effects**
  - Injection site reactions
  - Increases in ALT and/or AST levels
Rationale for Use of Tocilizumab Persons with COVID-19

• Elevated levels of inflammatory cytokines, including IL-6 have been associated with increased mortality from ARDS
• Patients with COVID-19 have elevated levels of IL-6 and other inflammatory markers consistent with cytokine storm
• Tocilizumab has been effective in treating the cytokine storm associated with CAR-T cell therapy

Source:
Tocilizumab: Recombinant Humanized Anti-IL6 Receptor Monoclonal Antibody

Mouse Monoclonal Antibody

Mouse variable region
Mouse constant region

Humanized Monoclonal Antibody

Human heavy chain
Human light chain
Complementary Determining Region

Illustration: David H. Spach, MD
Tocilizumab (Actemra)

Humanized Murine Monoclonal Antibody IgG1 Subclass

Binds to:
- Soluble IL-6 receptor
- Membrane bound IL-6 receptor

Illustration: David H. Spach, MD
IL-6 Signaling via Membrane IL-6 Receptor: Classic IL-6 Pathway

Host Cell

Membrane IL-6 Receptor

gp130

Recruitment of gp130

Signal Transduction

Illustration: David H. Spach, MD
IL-6 Signaling via Membrane IL-6 Receptor:
Classic IL-6 Pathway – Image Series (1 of 3)
IL-6 Signaling via Membrane IL-6 Receptor: Classic IL-6 Pathway – Image Series (2 of 3)

Host Cell

Illustration: David H. Spach, MD
IL-6 Signaling via Membrane IL-6 Receptor: Classic IL-6 Pathway – Image Series (3 of 3)

Host Cell

Illustration: David H. Spach, MD
IL-6 Signaling via Membrane IL-6 Receptor: Trans Signaling IL-6 Pathway

- IL-6 and Soluble IL-6 Receptor Complex
- Soluble IL-6 Receptor
- gp130

Signal Transduction

Illustration: David H. Spach, MD
IL-6 Signaling via Membrane IL-6 Receptor: Trans Signaling IL-6 Pathway – Image Series (1 of 4)

Host Cell

Soluble IL-6 Receptor

ADAM-10
ADAM-17

Illustration: David H. Spach, MD
IL-6 Signaling via Membrane IL-6 Receptor: Trans Signaling IL-6 Pathway – Image Series (2 of 4)

Illustration: David H. Spach, MD
IL-6 Signaling via Membrane IL-6 Receptor: Trans Signaling IL-6 Pathway – Image Series (3 of 4)

IL-6 and Soluble IL-6 Receptor Complex

IL-6

Soluble IL-6 Receptor

Host Cell

ADAM-10
ADAM-17

gp130

Illustration: David H. Spach, MD
IL-6 Signaling via Membrane IL-6 Receptor: Trans Signaling IL-6 Pathway – Image Series (4 of 4)

IL-6 and Soluble IL-6 Receptor Complex

Soluble IL-6 Receptor

ADAM-10, ADAM-17

Host Cell

gp130

Signal Transduction

Illustration: David H. Spach, MD
Tocilizumab Binds to Both Soluble and Membrane IL-6 Receptors

Host Cell

Tocilizumab

Soluble IL-6 Receptor

gp130

Membrane IL-6 Receptor

gp130

Illustration: David H. Spach, MD
Tocilizumab and Inhibition of IL-6 Signaling

Soluble IL-6 Receptor: Trans Signaling Pathway

Membrane Bound IL-6 Receptor: Classic Pathway

Host Cell

Signal Transduction
Tocilizumab Treatment of 15 Patients with COVID-19: A Single Center Experience (China)

Tocilizumab Treatment of 15 Patients with COVID-19: Study Design

<table>
<thead>
<tr>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong>: Retrospective case series study of 15 patients with variable severity of COVID-19 disease who received one or more doses of tocilizumab, with or without methylprednisolone during January 27–March 5, 2020 in China</td>
</tr>
<tr>
<td><strong>Setting</strong>: Wuhan, China</td>
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<tr>
<td><strong>Inclusion Criteria for Patients</strong></td>
</tr>
<tr>
<td>- Infected with SARS-CoV-2/COVID-19</td>
</tr>
<tr>
<td>- Received tocilizumab treatment</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>- 1 or more doses of intravenous tocilizumab: 80-600 mg per dose*</td>
</tr>
<tr>
<td>- Option to receive methylprednisolone^</td>
</tr>
</tbody>
</table>

*5 patients received >1 dose of tocilizumab (3 received 2 doses and 2 received 3 doses) |
^8 of 15 received methylprednisolone (range 4 to 7 days) of treatment |

## Tocilizumab Treatment of 15 Patients with COVID-19: Patient Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Patients (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range), years</td>
<td>73 (62 – 80)</td>
</tr>
<tr>
<td>Male, Female</td>
<td>12, 3</td>
</tr>
<tr>
<td>Clinical Status*</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td>Severe</td>
<td>6</td>
</tr>
<tr>
<td>Critical</td>
<td>7</td>
</tr>
<tr>
<td>Comorbidities (HTN, CVD, DM)</td>
<td>10</td>
</tr>
<tr>
<td>Also received methylprednisolone</td>
<td>8</td>
</tr>
</tbody>
</table>

*Defined by guidance Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus issued by the National Health Commission of China

Tocilizumab Treatment of 15 Patients with COVID-19: Results

- 3 of 7 critically ill patients progressed to death despite therapy
- 2 patients experienced worsening of their illness
- CRP levels decreased in 14 of 15 patients
- IL-6 levels remained persistently elevated in 1 seriously ill and 4 critically ill patients, including the 3 who died
- IL-6 levels initially spiked after tocilizumab and then decreased in all patients experiencing clinical stabilization or improvement

Conclusions: “Tocilizumab appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storms. And for these critically ill patients with elevated IL-6, repeated dose of the Tocilizumab is recommended.”
Tocilizumab Treatment of 21 Patients with Severe COVID-19 (China)

Tocilizumab Treatment of 21 Patients with Severe COVID-19: Design

<table>
<thead>
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<tbody>
<tr>
<td><strong>Background:</strong> Uncontrolled, observational study to evaluate the effectiveness of intravenous tocilizumab in patients with severe COVID-19 in Wuhan, China during February 5 – February 14, 2020.</td>
</tr>
<tr>
<td><strong>Inclusion Criteria (n = 21)</strong></td>
</tr>
<tr>
<td>- PCR-confirmed SARS-CoV-2 infection on throat swab</td>
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<tr>
<td>- Severe COVID-19 (any of following):</td>
</tr>
<tr>
<td>- RR ≥ 30/min or SpO₂ ≤93% on room air or PaO₂/FiO₂ ≤300 mm Hg</td>
</tr>
<tr>
<td>- Critical COVID-19 (any of following):</td>
</tr>
<tr>
<td>- Mechanical ventilation or shock or multiorgan failure plus ICU admit</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>- Tocilizumab: 400 mg intravenous infusion x 1 plus</td>
</tr>
<tr>
<td>- Standard of care at hospital: lopinavir, methylprednisolone, supportive care</td>
</tr>
</tbody>
</table>

## Tocilizumab Treatment of 21 Patients with Severe COVID-19: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic*</th>
<th>Patients (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (range)</td>
<td>56.8 ± 16.5 (25-88)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>18 (85.7)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>9 (42.9)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Illness Severity</td>
<td></td>
</tr>
<tr>
<td>Severe, n (%)</td>
<td>17 (81)</td>
</tr>
<tr>
<td>Critical, n (%)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Pretreatment IL-6, mean ± SD*</td>
<td>132.38 ± 278.54 pg/mL</td>
</tr>
</tbody>
</table>

## Tocilizumab Treatment of 21 Patients with Severe COVID-19: Baseline Characteristics

<table>
<thead>
<tr>
<th>Laboratory Markers of Inflammation</th>
<th>Before</th>
<th>Day 1 after Tocilizumab</th>
<th>Day 5 after Tocilizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (x 10^9/L)</td>
<td>6.30 ± 2.77</td>
<td>8.05 ± 4.39</td>
<td>5.25 ± 2.11</td>
</tr>
<tr>
<td>Lymphocyte percentage</td>
<td>15.52 ± 8.89</td>
<td>11.78 ± 11.36</td>
<td>22.62 ± 13.48</td>
</tr>
<tr>
<td>CRP</td>
<td>75.06 ± 66.80</td>
<td>38.13 ± 54.21</td>
<td>2.72 ± 3.60</td>
</tr>
<tr>
<td>Procalcitonin, ng/mL</td>
<td>0.33 ± 0.78</td>
<td>0.21 ± 0.35</td>
<td>0.12 ± 0.15</td>
</tr>
<tr>
<td>Interleukin-6, pg/mL</td>
<td>153.44 ± 296.63</td>
<td>129.18 ± 131.79</td>
<td>274.90 ± 414.08</td>
</tr>
</tbody>
</table>

Tocilizumab Treatment of 21 Patients with Severe COVID-19: Results

- Fever in all patients resolved on day 1 after tocilizumab infusion
- 21 of 21 (100%) experienced improvement in SpO2 and/or ventilator requirements
- 15 of 20 (75%) had lower O₂ intake <5 days after tocilizumab
- 21 of 21 (100%) discharged from hospital
- Mean hospitalization time 15.1 ± 5.8 days after tocilizumab

**Conclusion:** “Preliminary data show that tocilizumab, which improved the clinical outcome immediately in severe and critical COVID-19 patients, is an effective treatment to reduce mortality.”