Tocilizumab did not reduce hypoxemic respiratory failure or death in hospitalized patients with COVID-19


Question: In moderately ill hospitalized patients with coronavirus disease 2019 (COVID-19), does tocilizumab reduce risk for hypoxemic respiratory failure or death?


Blinding: Treatment allocation concealed; blinded (patients, investigators, and study coordinators).*

Setting: 7 hospitals in Boston, Massachusetts, USA.

Patients: 243 patients aged 19 to 85 years (median age, 60 y; 58% men) who had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by nasopharyngeal swab reverse transcriptase polymerase chain reaction or serum immunoglobulin M antibody assay; ≥2 of body temperature >3⁸ °C within 72 hours before enrollment, pulmonary infiltrates, or need for supplemental oxygen to maintain an oxygen saturation >92%; and ≥1 of C-reactive protein >50 mg/L, ferritin >500 ng/mL, D-dimer >1000 ng/mL, or lactate dehydrogenase >250 U/L. Key exclusions: receipt of supplemental oxygen at a rate >10 L/min, recent history of treatment with biologic agents or small molecule immunosuppressive therapy, receipt of other immunosuppressive therapy believed to increase risk for infection, or diverticulitis.

Interventions: A single dose of IV tocilizumab, 8 mg/kg up to 800 mg (n = 161), or placebo (n = 82) added to usual care.

Funding: Genentech.

Results: Tocilizumab vs. placebo in moderately ill hospitalized patients with COVID-19 (modified intention-to-treat analysis)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Event rates</th>
<th>RRR/RRI/RBR (95% CI) at 28 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation or death</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>6.8%</td>
<td>10%</td>
</tr>
<tr>
<td>Death</td>
<td>5.6%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Discontinuation of supplemental oxygen in patients receiving it at baseline</td>
<td>83%</td>
<td>85%</td>
</tr>
<tr>
<td>Clinical worsening</td>
<td>19%</td>
<td>17%</td>
</tr>
</tbody>
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Tocilizumab increased risk for grade ≥3 neutropenia (14% vs. 1%; P = 0.002) and reduced risk for grade ≥3 infection (8.1% vs. 17%; P = 0.03).

Commentary: The well-designed randomized controlled BACC trial conducted by Stone and colleagues and funded by Genentech assessed the effect of tocilizumab on hospitalized, non-critically ill patients with COVID-19. They found no effect on the primary outcome, a composite of intubation or death, although the hazard ratio’s wide confidence intervals do not rule out important benefit or harm. The sample size for this trial was calculated assuming a baseline risk of 30% for the composite outcome at 28 days and that tocilizumab would reduce this absolute risk to 15%. With a much lower observed risk than was anticipated (13% in the placebo group), the trial was underpowered to detect meaningful differences between the treatment groups.

Hyperinflammation and exaggerated host immune response are responsible for much of the pathology associated with SARS-CoV-2 infection. Patients with severe disease have elevated inflammatory markers, including interleukin 6 (IL-6), and there is good rationale for using targeted anti-inflammatory agents, such as tocilizumab. Much of the previous data examining this drug is found in treatment of cytokine release syndrome in patients having chimeric antigen receptor T-cell therapy (1).

In contrast to the BACC trial, early reports from the REMAP-CAP platform trial suggests possible benefit with tocilizumab in patients who are severely ill with COVID-19 in the intensive care unit (2). Given the pathophysiology of COVID-19 and the rationale for using an IL-6 inhibitor in cytokine release syndrome, it may be more beneficial to use tocilizumab later in the course of illness, when inflammation, rather than viral replication, is more implicated. On the other hand, IL-6 may be just one of many inflammatory markers, and therefore, targeting it in isolation may not lead to clinical improvement (3).

Given the benefit of steroid therapy (4) and the equivocal and conflicting results for the more costly tocilizumab, it is difficult to rationalize widespread use of tocilizumab without further study. Clinical trials should also determine whether steroids and tocilizumab work on similar pathways and have a synergistic effect when combined.

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References

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