Should interleukin-6 (IL-6) inhibitors be used for COVID-19?

This write-up summarises a rapid evidence review of interleukin-6 (IL-6) inhibitors, particularly tocilizumab, to manage symptoms of patients with COVID-19. The information may be revised as new evidence emerges.

Background

The 7th edition of the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment published by China National Health Commission on 4 March 20201 included tocilizumab (IL-6 receptor inhibitor) as an option for patients with severe COVID-19, extensive lung lesions and elevated IL-6 levels. This was following reports of positive outcomes from the use of tocilizumab to control dangerous lung inflammation in 21 patients with severe COVID-19 in China.2,4

Clinical experts have observed that many patients with severe COVID-19 appear to have features of cytokine storm syndrome.5-8 Some have hypothesised that tocilizumab, which is licensed in the US and Europe for chimeric antigen receptor T (CAR-T)-cell-induced severe or life-threatening cytokine release syndrome, may be effective in a subgroup of patients who have cytokine storm syndrome associated with severe COVID-19.9,10

Subsequently, tocilizumab, sarilumab and siltuximab, which are commercially available IL-6 inhibitors, have been cited in media articles as potential treatment options for COVID-19.11, 12 Twelve other IL-6 inhibitors are in clinical or preclinical development.13

Clinical evidence

No published clinical trials were identified assessing the efficacy and safety of IL-6 inhibitors in managing COVID-19. In a case series of 21 patients with severe or critical COVID-19 pneumonia treated with tocilizumab, body temperatures of all patients returned to normal after one day. Peripheral oxygen saturation, inflammatory markers, and chest computed tomography scans showed improvement within a week for the majority.4

Based on results of a systematic review and meta-analysis of RCTs conducted in patients with rheumatoid arthritis, tocilizumab is associated with an increased risk of infectious respiratory adverse events (relative risk 1.53, 95% confidence interval 1.04 to 2.25).14 Both tocilizumab and sarilumab carry FDA black box warnings of serious infections leading to hospitalisation or death due to tuberculosis, bacterial, invasive fungal, viral, and other infections.

Table 1: Ongoing or planned studies for IL-6 inhibitors in patients with COVID-19

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Date of primary completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04315480,15</td>
<td>Single arm, OL, SC, phll, two-stage study</td>
<td>Tocilizumab</td>
<td>-</td>
<td>April 2020</td>
</tr>
<tr>
<td>NCT04310228,16</td>
<td>MC, OL, RCT (3 arms)</td>
<td>Favipiravir combined with tocilizumab</td>
<td>Favipiravir alone, Tocilizumab alone</td>
<td>May 2020</td>
</tr>
<tr>
<td>ChICTR2000030894,17</td>
<td>MC, OL, RCT</td>
<td>Tocilizumab with conventional therapy</td>
<td>Conventional therapy</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04306705,18</td>
<td>Retrospective cohort study (3 arms)</td>
<td>Tocilizumab with standard of care</td>
<td>Continuous renal replacement therapy with standard of care, Standard of care</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04322188,19</td>
<td>Observational, case-control study</td>
<td>Siltuximab</td>
<td>Standard of care</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04329650,20</td>
<td>SC, OL, phll, RCT</td>
<td>Siltuximab</td>
<td>Methylprednisolone</td>
<td>May 2020</td>
</tr>
<tr>
<td>NCT04333914,21</td>
<td>MC, OL, phll, RCT</td>
<td>Chloroquine analog (GNS651), Nivolumab, Tocilizumab</td>
<td>Standard of care</td>
<td>June 2020</td>
</tr>
<tr>
<td>NCT04327388,22</td>
<td>DB, phll/III, RCT</td>
<td>Sarilumab</td>
<td>Placebo</td>
<td>July 2020</td>
</tr>
</tbody>
</table>
None of the IL-6 inhibitors are mentioned by WHO in its interim guidance on the clinical management of COVID-19 infection. The Society of Critical Care Medicine and the European Society of Intensive Care Medicine has stated that there is insufficient evidence to issue a recommendation on the use of tocilizumab in critically ill adults with COVID-19. The interim clinical guidance for adults with suspected or confirmed COVID-19 in Belgium (version 6) has recommended that tocilizumab only be evaluated in clinical trials. Similarly, the Ministry of Health in Spain identified tocilizumab and sarilumab as potential therapeutic strategies, and stated that their use should be through clinical studies.

While acknowledging the paucity of scientific evidence, a number of professional bodies have included tocilizumab as a treatment option for selected patients with severe COVID-19:

- **Chinese Clinical Guidance for COVID-19**: recommended that tocilizumab may be tried for patients with extensive and bilateral lung lesions who are severely ill with elevated IL-6 levels, without active infections such as tuberculosis.
- **The Italian Society of Infectious Diseases and Tropical Diseases COVID-19 Guideline**: has recommended the use of tocilizumab in carefully selected patients who develop acute respiratory distress syndrome.
- **Michigan Medicine (University of Michigan)** listed tocilizumab as an investigational therapeutic and stated that it should be reserved for compassionate use. A decision to use it must be made with close attention to the patient’s clinical status, comorbidities and interacting medicines.
- **The Society for Immunotherapy of Cancer**: has stated that the availability of IL-6 inhibitors should be maximised for use on a compassionate basis for hospitalised, critically ill COVID-19 patients.

### Recommendations from professional bodies

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Design</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Phase</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04331795</td>
<td>SC, OL, non-randomised study</td>
<td>Tocilizumab 200mg*</td>
<td>Placebo</td>
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<td>July 2020</td>
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<tr>
<td>NCT04330638</td>
<td>OL, MC, factorial design RCT</td>
<td>Tocilizumab</td>
<td>Usual care</td>
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<td>September 2020</td>
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<tr>
<td>NCT04332094</td>
<td>MC, OL, RCT</td>
<td>Hydroxychloroquine</td>
<td>Placebo</td>
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<td>September 2020</td>
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<tr>
<td>NCT04332913</td>
<td>Observational cohort study</td>
<td>Tocilizumab</td>
<td>Placebo</td>
<td></td>
<td>December 2020</td>
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<tr>
<td>NCT04317092</td>
<td>Single-arm, MC, observational</td>
<td>Tocilizumab</td>
<td>Placebo</td>
<td></td>
<td>December 2020</td>
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<tr>
<td>NCT04321993</td>
<td>OL, non-randomised study</td>
<td>Tocilizumab</td>
<td>-</td>
<td></td>
<td>February 2021</td>
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<tr>
<td>NCT04315298</td>
<td>DB, RCT (3 arms)</td>
<td>High dose sarilumab</td>
<td>Placebo</td>
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<td>March 2021</td>
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<tr>
<td>NCT0434073</td>
<td>OL, cmRCT</td>
<td>Sarilumab</td>
<td>Standard of care</td>
<td></td>
<td>March 2021</td>
</tr>
<tr>
<td>NCT04331800</td>
<td>OL, phII/III, RCT</td>
<td>Tocilizumab</td>
<td>Standard of care</td>
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<td>March 2021</td>
</tr>
<tr>
<td>NCT04322773</td>
<td>MC, OL, RCT</td>
<td>IV tocilizumab</td>
<td>Standard of care</td>
<td></td>
<td>June 2021</td>
</tr>
<tr>
<td>NCT04320615</td>
<td>MC, DB, phIII, RCT</td>
<td>Tocilizumab</td>
<td>Placebo</td>
<td></td>
<td>August 2021</td>
</tr>
</tbody>
</table>

**Abbreviations:** cmRCT, cohort multiple randomised controlled trial; DB, double blind; IV, intravenous; MC, multicenter; OL, open label; RCT, randomised controlled trial; phII, phase II; phIII, phase III; phIV, phase IV; SC, single centre; SO, subcutaneous

*Italy *Spain *A second series of patients will be treated only if the first series of recruited patients demonstrate response *United States *For hospitalised, non-critically ill patients with COVID-19 pneumonitis with risk factors for decompensation *For hospitalised, non-critically ill patients with COVID-19 pneumonitis without risk factors for decompensation
Conclusion

There is a lack of evidence evaluating the efficacy and safety of tocilizumab or other IL-6 inhibitors to manage patients with severe COVID-19. Further data from ongoing and planned clinical trials is needed to confirm the role of IL-6 inhibitors in the management of patients with COVID-19.

References


11. Siegel ER. Here are some of the existing drugs that may be repurposed to treat coronavirus: NBC News; [cited 20 March 2020]. Available from: https://www.nbcnews.com/health/health-news/heres-some-existing-drugs-may-be-repurposed-treat-coronavirus-n1162051


36. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected (Interim guidance V1.2). World Health Organisation.


