

# 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 7<sup>th</sup> edition of the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment published by China National Health Commission on 4 March 2020<sup>1</sup> 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.<sup>2-4</sup>

Clinical experts have observed that many patients with severe COVID-19 appear to have features of cytokine storm syndrome.<sup>5, 6</sup> 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.<sup>7, 8</sup>

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.<sup>9, 10</sup> Twelve other IL-6 inhibitors are in clinical or preclinical development.<sup>11</sup>

## 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.<sup>4</sup>

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).<sup>12</sup> 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**

Study identifier	Study Design	Intervention	Comparator	Date of primary completion
NCT04310228 <sup>13</sup>	MC, OL, RCT (3 arms)	favipiravir combined with tocilizumab	<ul style="list-style-type: none"><li>favipiravir alone</li><li>tocilizumab alone</li></ul>	May 2020
NCT04306705 <sup>14</sup>	Retrospective cohort study (3 arms)	tocilizumab with standard of care	<ul style="list-style-type: none"><li>continuous renal replacement therapy with standard of care</li><li>standard of care alone</li></ul>	May 2020
NCT04322188 <sup>15</sup>	Observational, case-control study	siltuximab	standard of care	May 2020
NCT04317092 <sup>16</sup>	Single-arm, MC, pII, observational cohort study	tocilizumab	-	December 2020

NCT04321993 <sup>17</sup>	OL, pHII, non-randomised study	<ul style="list-style-type: none"> <li>• lopinavir/ritonavir</li> <li>• hydroxychloroquine sulfate</li> <li>• baricitinib</li> <li>• sarilumab</li> </ul>	-	February 2021
NCT04315298 <sup>18</sup>	DB, pHII/III, RCT (3 arms)	<ul style="list-style-type: none"> <li>• high dose sarilumab</li> <li>• low dose sarilumab</li> </ul>	Placebo	March 2021
NCT04322773 <sup>19</sup>	MC, OL, RCT (4 arms)	<ul style="list-style-type: none"> <li>• intravenous tocilizumab</li> <li>• subcutaneous tocilizumab</li> <li>• subcutaneous sarilumab</li> </ul>	standard medical care	June 2021
NCT04320615 <sup>20</sup>	MC, DB, pHIII, RCT	tocilizumab	Placebo	August 2021

Abbreviations: DB, double blind; MC, multicenter; OL, open label; RCT, randomised controlled trial; pHII, phase II; pHIII, phase III

## Recommendations from professional bodies

None of the IL-6 inhibitors are mentioned by WHO in its interim guidance on the clinical management of COVID-19 infection.<sup>21</sup> Also, 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.<sup>22</sup>

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<sup>1</sup> 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<sup>23</sup> has recommended the use of tocilizumab in carefully selected patients who develop acute respiratory distress syndrome. This was based on the observed similarity in clinical manifestations to cytokine release syndrome, as well as reported clinical response in 21 patients who received tocilizumab in China.
- Michigan Medicine (University of Michigan)<sup>24</sup> 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<sup>25</sup> has stated that the availability of IL-6 inhibitors should be maximised for use on a compassionate basis for hospitalised, critically ill COVID-19 infected patients. This was based on the established efficacy of tocilizumab in CAR-T cell-induced cytokine release syndrome, as well as clinical evidence which suggests that tocilizumab reduces immune checkpoint inhibitor-induced toxicity in patients who are steroid-refractory.

## 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.

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