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

This clinical evidence summary outlines existing evidence on the use of interleukin-6 (IL-6) inhibitors to manage symptoms of patients with COVID-19. The information may be revised as new evidence emerges. The summary is not exhaustive of the subject matter and does not replace clinical judgement. The responsibility for making decisions appropriate to the circumstances of the individual patient remains at all times with the healthcare professional.

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 2020[1] 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] A preprint systematic review and meta-analysis by Coomes et al.[9] of six observational cohort studies on patients with COVID-19 (n=1302) found that IL-6 levels in patients with complicated disease were significantly higher than in patients with non-complicated disease (ratio of means 2.90, 95% confidence interval 1.17 to 7.19). 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 (CRS), may be effective in a subgroup of patients who have cytokine storm syndrome associated with severe COVID-19.[10, 11]

Tocilizumab, sarilumab and siltuximab, have been cited in media articles as potential treatment options for COVID-19.[12, 13] Twelve other IL-6 inhibitors are in clinical or preclinical development.[14]

Clinical evidence

There is limited high quality published evidence for the use of IL-6 inhibitors to treat COVID-19:

Tocilizumab (IL-6 receptor inhibitor)

Evidence suggesting clinical benefit:

- In a pilot study of 21 patients with severe or critical COVID-19 pneumonia treated with tocilizumab plus standard of care, body temperatures of all patients returned to normal after one day. Peripheral oxygen saturation, inflammatory markers, and chest computed tomography (CT) scans showed improvement within a week for the majority.[4, 15]
- Results of the CORIMUNO-19 (NCT04331808) multicentre, open-label, randomised controlled trial (RCT) comparing tocilizumab and standard of care (n=65) with standard of care alone (n=64) were summarised in a press release.[16] A significantly lower proportion of patients in the tocilizumab arm required ventilation or died at day 14. Further details have not been published.
- In a retrospective study of 544 patients (tocilizumab n=179, standard of care n=365) with severe COVID-19 pneumonia[17], tocilizumab was associated with a reduced risk of death (HR 0.38, 95%CI 0.40 to 0.92), as well as the composite endpoint of mechanical ventilation initiation or death (HR 0.61, 95%CI 0.40 to 0.92), compared with standard of care.
- In a preprint observational study[18] of 154 patients with severe COVID-19 pneumonia who required invasive mechanical ventilation, tocilizumab was associated with a lower hazard of death compared with standard of care after inverse probability treatment weights adjustment (HR 0.54, 95%CI 0.35, 0.84). Patients who received tocilizumab were more than twice as likely to develop a superinfection than untreated controls (54% vs 26%, p<0.001), driven primarily by a large increase in ventilator-associated pneumonia (45% vs 20%, p<0.001).

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- Twelve patients who had severe COVID-19 received 2-4 doses of 162mg subcutaneous tocilizumab and standard therapy in a retrospective observational study.[19] At presentation, two patients had grade 1 CRS, five patients had grade 2 CRS, and five patients had grade 3 CRS. By day 7, median levels of inflammatory markers, including C-reactive protein (CRP) and IL-6, were improved, and none of the patients had grade 4 CRS.
- Case reports of patients with concomitant severe COVID-19 and cancer showed improvement in oxygen saturation and chest CT scans following administration of tocilizumab.[20, 21]

Evidence suggesting no clinical benefit:

- The COVID-BioB retrospective study (NCT04318366)[22] compared tocilizumab plus standard of care with standard of care alone (hydroxychloroquine, lopinavir/ritonavir, antibiotics, enoxaparin) among 65 patients with severe COVID-19. At day 28 there were no significant differences in clinical outcomes, hospital discharges, or mortality.
- The Italian Medicines Agency (AIFA) issued a press release[23] reporting that an RCT (NCT04346355) which compared the efficacy of early administration of tocilizumab vs standard therapy for patients with COVID-19 who did not require mechanical ventilation was terminated early after no benefit was shown in terms of intensive care requirement and 30-day survival.

Sarilumab (IL-6 receptor inhibitor)

- Preliminary results from an ongoing phase II/III trial (NCT04315298) which compared a single dose of sarilumab (200mg or 400mg) with placebo in patients with severe or critical COVID-19 (n=457) were announced in a press release.[24] The study demonstrated a reduction in CRP levels with sarilumab treatment. Exploratory analyses found a positive trend in clinical outcomes only in patients with critical disease. Thus, the independent data monitoring committee recommended that only patients with critical disease continue to be enrolled to receive sarilumab 400mg or placebo. No new safety signals were observed.
- A preprint observational cohort study reported clinical outcomes of 53 patients with severe COVID-19 pneumonia treated with 1-2 doses of sarilumab.[25] The majority of patients received concomitant antiviral therapy and hydroxychloroquine. At a median follow-up of 19 days, 89.7% of patients hospitalised in the medical ward had significant clinical improvement, 70.6% were discharged, and one died. Of patients warded in the intensive care unit, 64.3% no longer needed oxygen supplementation within 5-12 days, and two patients died.

Siltuximab (IL-6 inhibitor)

- In a preprint observational study (NCT04322188), 21 patients with COVID-19 who developed pneumonia or acute respiratory distress syndrome received treatment with siltuximab.[26, 27] At seven days, all patients experienced decreased CRP levels, seven (33%) experienced clinical improvement and nine (43%) had no clinically relevant changes. A worsening of disease was seen in three patients (14%), and one died.

Both tocilizumab and sarilumab have US FDA black box warnings of serious infections leading to hospitalisation or death due to tuberculosis, bacterial, invasive fungal, viral, and other infections. Frigault et al. (2020)[28] found no difference in the incidence of clinically significant infections or infectious density within 100 days of treatment between patients who received tocilizumab for CAR-T-related CRS and patients who did not receive tocilizumab (31% vs 30%, p=0.85). This suggests that infectious complications observed during long-term use of IL-6 inhibitors may not be relevant to a much shorter treatment course for COVID-19 pneumonia.

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

Study identifier	Study Design	Intervention	Comparator	Date of primary completion
NCT04310228[29] ChiCTR2000030894[30]	MC, OL, RCT (3 arms)	Favipiravir combined with tocilizumab	• Favipiravir alone • Tocilizumab alone	May 2020
NCT04341870[31]	MC, OL, phII/IIII, RCT	Sarilumab, azithromycin and hydroxychloroquine	Sarilumab	May 2020
NCT04335305[32]	MC, OL, phII, RCT	Tocilizumab with pembrolizumab	Standard of care	May 2020
ChiCTR2000029765[33]	MC, phIV, RCT	Tocilizumab with conventional therapy	Conventional therapy	May 2020
NCT04329650[29] EudraCT 2020-001413-20[34]	SC~, OL, phII, RCT	Siltuximab	Methylprednisolone	May 2020
NCT04346355[30]	MC, OL, phII, RCT	Tocilizumab and standard of care	Standard of care	May 2020
NCT04333914 [35]	MC, OL, phII, RCT	• Chloroquine analog (GNS651) • Nivolumab • Tocilizumab	Standard of care	June 2020
NCT04356937[36]	MC, DB, phIII, RCT	Tocilizumab	Placebo	June 2020
NCT04363736[37]	MC, OL, phII, RCT	Tocilizumab 8mg/kg	Tocilizumab 4mg/kg	June 2020
NCT04357808[38]	SC~, OL, phII, RCT	Sarilumab and standard of care	Standard of care	June 2020
NCT04327388[39]	DB, phII/III, RCT	Sarilumab	Placebo	July 2020
NCT04357860[40]	SC~, OL, phII, RCT	• Sarilumab 200mg • Sarilumab 400mg	Placebo	July 2020
NCT04403685[41]	MC, OL, phIII, RCT	• Tocilizumab and best supportive care	Best supportive care	July 2020
NCT04409262[42]	MC, DB, phIII, RCT	• Remdesivir • Tocilizumab	Placebo	July 2020
NCT04372186[43]	MC, DB, phIII, RCT	Tocilizumab	Placebo	August 2020
NCT04320615[44]	MC, DB, phIII, RCT	Tocilizumab	Placebo	August 2020
NCT04377503[45]	OL, phII, crossover RCT	Tocilizumab	Methylprednisolone	August 2020
NCT04412291[46]	SC◊, OL, phII, RCT	• Anakinra • Tocilizumab	Standard of care	August 2020
NCT04435717[47]	SC~, OL, phII, RCT	• Tocilizumab 8mg/kg in a single dose • Tocilizumab 8mg/kg in 2 doses	Standard of care	August 2020
NCT04330638[48] EudraCT 2020-001500-41[49]	OL, MC, phIV, factorial design RCT (6 arms)	• Anakinra • Siltuximab • Anakinra and siltuximab • Tocilizumab • Anakinra and tocilizumab	Usual care	September 2020
NCT04332094[50]	MC, OL, phII, RCT	Tocilizumab, hydroxychloroquine and azithromycin	Hydroxychloroquine and azithromycin	September 2020
NCT04361032[51]	MC, OL, phIII, RCT	Tocilizumab, enoxaparin and standard of care	Deferoxamine, enoxaparin and standard of care	September 2020
NCT04335071[52]	MC, DB, phII, RCT	Tocilizumab	Placebo	October 2020
NCT04345445[53]	SC‖, OL, crossover, RCT	• Tocilizumab • Methylprednisolone	-	October 2020
NCT04381936[54] EudraCT2020-001113-21[55]	MC, OL, phII/III, RCT	• Lopinavir-ritonavir • Low dose corticosteroids • Hydroxychloroquine • Azithromycin • Tocilizumab	Standard of care	December 2020
NCT04315298[56]	DB, phII/III, RCT (3 arms)	• High dose sarilumab • Low dose sarilumab	Placebo	March 2021
NCT04324073[57]	OL, phII/III, cmRCT	Sarilumab	Standard of care	March 2021
NCT04331808[58]	OL, phII, cmRCT	Tocilizumab	Standard of care	March 2021
NCT04377659[59]	OL, phII, RCT	Tocilizumab	Placebo	May 2021
NCT04377750[60]	MC, OL, phIV, RCT	Tocilizumab	Placebo	May 2021
NCT04322773[61] EudraCT 2020-001275-32[62]	MC, OL, phII, RCT (4 arms)	• IV tocilizumab • SQ tocilizumab • SQ sarilumab	Standard of care	June 2021

NCT04345289[63]	MC, DB, phIII, RCT (6 arms)	• Convalescent plasma • Sarilumab • Hydroxychloroquine • Baricitinib	• Injective placebo • Oral placebo	June 2021
NCT04412772[64]	SC*, DB, phIII, RCT	Tocilizumab	Placebo	December 2021
NCT04361552[65]	SC*, OL, phIII, RCT	Tocilizumab and standard of care	Standard of care	May 2022
NCT04359901[59]	SC*, OL, phII, RCT	Sarilumab and standard of care	Standard of care	April 2022
NCT04424056[66]	SC^, OL, phIII, RCT	• Anakinra +/- ruxolitinib (stages 2b/3) • Anakinra and ruxolitinib (advanced stage 3) • Tocilizumab +/- ruxolitinib (stages 2b/3) • Tocilizumab and ruxolitinib (advanced stage 3)	Standard of care	September 2022
ChiCTR2000030580[67]	SC▲, OL, RCT	Tocilizumab and adalimumab	Standard of care	-
EudraCT 2020-001770-30[68]	MC, OL, phII, RCT	Tocilizumab	Standard of care	-
EudraCT 2020-001408-41[69]	SC**, DB, phII, RCT	Tocilizumab	Placebo	-
EudraCT 2020-002037-15[70]	SC¯, OL, phII, RCT	Sarilumab	Placebo	-
EudraCT 2020-001634-36[71]	SC¯, OL, phII, RCT	Sarilumab and standard of care	Standard of care	-
EudraCT 2020-001039-29[72]	MC, OL, phII, RCT	Anakinra	Tocilizumab	-
EudraCT 2020-001386-37[73]	MC, OL, phII, RCT	Tocilizumab (early administration)	Tocilizuamb (late administration)	-
EudraCT 2020-001437-12[74]	SC¯, OL, phIV, RCT	• IV ciclosporin • Oral ciclosporin • IV tocilizumab	-	-
EudraCT 2020-002032-69[75]	SC¯, OL, phII, RCT	Tocilizumab	Standard of care	-
EudraCT 2020-001290-74[76]	SC¯, OL, phIII, RCT	Sarilumab	• Azithromycin • Hydroxychloroquine	-
EudraCT 2020-001854-23[77]	MC, OL, phII/III, RCT	• Hydroxychloroquine • Tocilizumab • Sarilumab • Siltuximab • Canakinumab • Baricitinib • Methylprednisolone	-	-

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; SQ, subcutaneous
¯Spain *United States **Germany ‖ Malaysia ▲China ^France ◊ Sweden

Recommendations from professional bodies

Interim guidance on the clinical management of COVID-19 by the World Health Organization (WHO)[78], Belgium[79], the Infectious Disease Society of America,[80] and Spain's Ministry of Health[81] recommend the use of IL-6 inhibitors only in the context of a clinical trial. The Society of Critical Care Medicine, the European Society of Intensive Care Medicine,[82] and the National Institutes of Health[83] state that there is insufficient evidence to issue a recommendation on the use of tocilizumab for COVID-19.

Several organisations have included IL-6 inhibitors in their treatment guidelines as an option for patients with severe COVID-19:

- Interim treatment guidelines for COVID-19 from the National Centre for Infectious Diseases (NCID) Singapore[84] do not recommend routine use of IL-6 inhibitors outside a trial setting but suggest that they may be considered in patients with cytokine storm or hyperinflammation, after careful discussion with multi-disciplinary input;

- Chinese Clinical Guidance for COVID-19[1] recommends 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[85] recommends the use of tocilizumab in carefully selected patients who develop acute respiratory distress syndrome;
- The Society for Immunotherapy of Cancer[86] has stated that the availability of IL-6 inhibitors should be maximised for compassionate use for hospitalised, critically ill COVID-19 patients;
- The Johns Hopkins Medical Institution (US) recommends that patients with COVID-19 and CRS at high risk of severe CRS may be considered for IL-6 inhibitor therapy if a clinical trial is not available and the patients meet specific clinical criteria. Tocilizumab is preferred over other IL-6 inhibitors despite very limited evidence of its benefits in the treatment of COVID-19.[87]

Conclusion

There is a lack of high-quality evidence evaluating the efficacy and safety of 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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