NICE advice

COVID-19 rapid evidence summary: Tocilizumab for COVID-19

Evidence summary
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www.nice.org.uk/guidance/es33

Product overview

The content of this evidence summary was up to date in February 2021. New evidence may have been published since then. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date prescribing information.

Tocilizumab is an interleukin-6 inhibitor. It has marketing authorisations for rheumatoid arthritis and giant cell arteritis in adults, systemic juvenile idiopathic arthritis and juvenile idiopathic polyarthritis in children 2 years and older, and chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome in adults, young people and children 2 years and older (see the summaries of product characteristics for tocilizumab). Use of tocilizumab for COVID-19 is off label.

Likely place in therapy

Preliminary evidence from Horby et al. (2021; the RECOVERY study) suggests that tocilizumab is

beneficial in adults who have been hospitalised with severe COVID-19 and have clinical evidence of progressive disease (hypoxia and systemic inflammation).

Preliminary evidence from Gordon et al. (2021; the REMAP-CAP study) suggests that tocilizumab is beneficial in adults with severe COVID-19 who are critically ill and receiving respiratory or cardiovascular organ support in an intensive care setting. Tocilizumab was given within about 24 hours of starting organ support.

In these populations, it is possible that any benefit is more likely with earlier use, when disease progression and any developing organ dysfunction may be more reversible.

There is an interim clinical commissioning policy from NHS England on tocilizumab for hospitalised patients with COVID-19 pneumonia (adults).

There is also a related NICE COVID-19 rapid evidence summary on sarilumab for COVID-19.

Factors for decision making

Effectiveness and safety

Evidence was from 5 published randomised controlled trials (RCTs) in adults hospitalised with COVID-19 pneumonia:

- Hermine et al. (2021; CORIMUNO-TOCI)
- Salama et al. (2021; EMPACTA)
- Salvarani et al. (2021; RCT-TCZ-COVID-19)
- Stone et al. (2020; BACC Bay Tocilizumab Trial)
- Veiga et al. (2021; TOCIBRAS).

It also included prepublication study results from Gordon et al. (2021; REMAP-CAP) and Horby et al. (2021; RECOVERY), which are nationally prioritised platform studies in adults who are hospitalised.

In Horby et al. (2021, n=4,116), patients had clinical evidence of progressive COVID-19. This was defined as hypoxia (oxygen saturation of less than 92% on room air or when receiving oxygen

therapy) and systemic inflammation (C-reactive protein [CRP] of 75 mg/litre or more). About 55% of patients were receiving non-invasive or mechanical ventilation. In Gordon et al. (2021, n=778), patients had severe COVID-19, were critically ill in an intensive care setting, and were receiving respiratory or cardiovascular organ support (72% receiving non-invasive or mechanical ventilation, all randomised within 24 hours of starting organ support).

In Salama et al. (2021, n=389), Salvarani et al. (2021, n=126), and Stone et al. (2020, n=243), patients had severe COVID-19, but were not receiving non-invasive or mechanical ventilation at baseline. In Hermine et al. (2021, n=131), patients had moderate or severe disease but were not receiving non-invasive or mechanical ventilation, and were not in intensive care. In Veiga et al. (2021, n=129), patients had severe or critical COVID-19, and were receiving oxygen or mechanical ventilation (for less than 24 hours).

Tocilizumab was given intravenously at an initial dose of 8 mg/kg in most studies. In Horby et al. (2021), the dose (800 mg, 600 mg or 400 mg) was determined by body weight bands. The maximum dose was 800 mg in all studies. A second dose was given at 12 hours in Salvarani et al. (2021). A second dose was given based on clinical worsening and the discretion of the clinician at 3 days in Hermine et al. (2021), at 12 to 24 hours in Horby et al. (2021) and Gordon et al. (2021), and at 8 to 24 hours in Salama et al. (2021). A single dose was given in Stone et al. (2020) and Veiga et al. (2021). The standard-care treatments used in the studies varied but all included corticosteroids in varying proportions of use. In Gordon et al. (2021) and Horby et al. (2021), corticosteroids were used in most patients (above 80%).

In Horby et al. (2021), there was a statistically significant reduction in mortality at 28 days in the tocilizumab group (596 of 2,022; 29%) compared with the standard-care group (694 of 2,094; 33%, rate ratio 0.86, 95% confidence interval [CI] 0.77 to 0.96, p=0.007). In patients not receiving mechanical ventilation at baseline, there was a statistically significant reduction in the combined outcome of mechanical ventilation or death with tocilizumab compared with standard care (33% compared with 38%, risk ratio 0.85, 95% CI 0.78 to 0.93, p=0.0005). However, there was no statistically significant difference in the combined outcome of non-invasive or mechanical ventilation at 28 days between the tocilizumab and standard-care groups in patients not receiving ventilation at baseline. In patients receiving mechanical ventilation at baseline, there was no statistically significant difference in successfully stopping mechanical ventilation at 28 days between the tocilizumab and standard-care groups. Statistically significant improvements in other outcomes were also seen with tocilizumab, including for haemodialysis or haemofiltration, and hospital discharge.

In Gordon et al. (2021), the median number of days free of organ support was statistically

significantly higher with tocilizumab compared with standard care (10 days, interquartile range [IQR] -1 to 16 compared with 0 days, IQR -1 to 15; median adjusted odds ratio [aOR] 1.64, 95% credible interval [CrI] 1.25 to 2.18, probability of superiority more than 99.9%). Days free of organ support includes death, where all deaths were assigned a value of -1. There were fewer in-hospital deaths in the tocilizumab group compared with the standard-care group (28.0% compared with 35.8%, median aOR for hospital survival 1.64, 95% CrI 1.14 to 2.35, probability of superiority more than 99.9%). Statistically significant improvements in other outcomes were also seen, including 90-day survival, time to discharge from intensive care and time to hospital discharge. In patients who were not intubated at baseline, statistically significantly fewer in the tocilizumab group compared with the standard-care group progressed to needing intubation or extracorporeal membrane oxygenation, or died.

The results from the 5 smaller RCTs were mixed. In Salama et al. (2021), there was a statistically significant decrease in the combined outcome of mechanical ventilation or death, and in time to clinical failure (death, mechanical ventilation or admission to intensive care) with tocilizumab compared with placebo. However, there was no statistically significant difference in mortality alone. In Salvarani et al. (2021), Stone et al. (2020) and Hermine et al. (2021), there were no statistically significant differences in outcomes related to death, ventilation or clinical status. In Veiga et al. (2021), there were no statistically significant differences between tocilizumab and standard care in the combined outcome of mechanical ventilation or death, mortality alone at 28 days, ventilator-free days, or time to independence from supplemental oxygen. There was, however, a statistically significant increase in mortality alone at 15 days and a statistically significant decrease in length of hospital stay in the tocilizumab group compared with the standard-care group.

In terms of safety, Horby et al. (2021) reported 3 serious adverse reactions believed to be related to tocilizumab: otitis externa, *Staphylococcus aureus* bacteraemia, and lung abscess. All resolved with standard treatment. No statistical analysis was reported. In Stone et al. (2020), there was a statistically significant increase in neutropenia but a counterintuitive decrease in serious infections with tocilizumab compared with placebo (p=0.002 and p=0.03 respectively). In the other studies, no statistically significant differences in adverse events or serious adverse events were reported between tocilizumab and placebo or standard care. However, most studies only had a 1-month follow-up period so longer-term safety outcomes of tocilizumab were not assessed.

See the summaries of product characteristics for tocilizumab for contraindications, cautions and a general summary of the safety profile.

Horby et al. (2021) reported prespecified subgroup analyses for the primary outcome of mortality

at 28 days for subgroups of age, sex, ethnicity, level of respiratory support, days since symptom onset and use of corticosteroids (including dexamethasone). There was a statistically significant reduction in mortality in the tocilizumab group compared with the standard-care group in people taking systemic corticosteroids, men, people from a white family background, and people with symptom onset in 7 days or less. There was no statistically significant difference in mortality between the 2 groups in any other reported subgroups, including age categories or respiratory support at randomisation.

Gordon et al. (2021) reported prespecified subgroup analyses by terciles of CRP, and similar effects were seen across all prespecified CRP subgroups.

In Stone et al. (2020), Salama et al. (2021) and Veiga et al. (2021), no statistically significant difference was seen between tocilizumab and standard care in subgroup analyses (including by age, sex, family background, obesity, diabetes and concomitant treatment).

Limitations of the evidence

In Horby et al. (2021; the RECOVERY study), use of tocilizumab was investigated in a broad range of patients who were hospitalised with severe COVID-19. Patients had clinical evidence of progressive COVID-19 (hypoxia and systemic inflammation). About 45% of patients received no ventilator support, 41% received non-invasive ventilation and 14% were mechanically ventilated. Results from this study substantially add to the evidence base for tocilizumab in COVID-19, with over 4,000 adults included in the study.

Gordon et al. (2021; the REMAP-CAP study) and Veiga et al. (2021) were the only other studies that included patients receiving mechanical ventilation (30% and 16%, respectively). In Gordon et al. (2021), patients were critically ill with severe COVID-19 and receiving organ support in an intensive care setting, and had to be enrolled within 24 hours of starting organ support. In Veiga et al. (2021), patients had severe or critical COVID-19, were receiving oxygen or mechanical ventilation (for less than 24 hours), and had at least 2 abnormal serum biomarkers. Hermine et al. (2021) included patients with moderate to severe COVID-19, and all other studies (Salama et al. 2020, Salvarani et al. 2021, and Stone et al. 2020) included patients with severe COVID-19. The definition of severe COVID-19 differed between these studies. All 7 included studies allowed concomitant standard care in both groups.

Risk of bias was rated as either 'some concerns' or 'low' for all the studies. Gordon et al. (2021), Hermine et al. (2021), Horby et al. (2021), Salvarani et al. (2021) and Veiga et al. (2021) were open-label studies. Gordon et al. (2021) and Horby et al. (2021) are large nationally prioritised platform

studies, but these data are preliminary, follow up is not complete, and the study results have not been peer reviewed.

Prespecified subgroup analyses in Horby et al. (2021) have suggested a mortality benefit particularly in people taking systemic corticosteroids, men, people from a white family background, and people with symptom onset in 7 days or less. No mortality benefits were seen in any other reported subgroups. However, it is difficult to draw firm conclusions because the results are based on multiple subgroup comparisons and any differences may be caused by chance. Gordon et al. (2021) reported prespecified subgroup analyses by terciles of CRP, and similar effects have been seen across all prespecified CRP subgroups.

Most of the studies had a 1-month follow-up period for the primary outcomes, and some patients were still in hospital at the time of reporting. Therefore, the longer-term effects of tocilizumab in COVID-19 are not known.

All included studies were in adults, so it is not possible to say what the efficacy or safety of tocilizumab is in children or young people.

See the full evidence review for more information.

Update information

24 February 2021: We updated the evidence summary at the request of NHS England because new evidence was identified: prepublication study results from the nationally prioritised platform study (Horby et al. 2021; the RECOVERY study), and a published randomised controlled trial (Veiga et al. 2021).

09 February 2021: We updated the link from NHS England's interim position statement to its interim clinical commissioning policy, which is now available.

Commissioned by NHS England.

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