NICE advice

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

Evidence summary
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Product overview

The content of this evidence summary was up to date in January 2021. 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 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

Unpublished preliminary evidence from the REMAP-CAP study has suggested that tocilizumab is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 (all randomised within 24 hours of starting organ support).

In adults hospitalised with moderate to severe or severe COVID-19 who were not receiving non-invasive or mechanical ventilation, results from 4 published randomised controlled trials were mixed.

It is possible that any benefit from tocilizumab is seen only in the most severely ill patients given tocilizumab soon after organ support is started, when any developing organ dysfunction may be more reversible.

There is an interim position statement from NHS England on interleukin-6 inhibitors (tocilizumab or sarilumab) for patients admitted to ICU with COVID-19 pneumonia (adults). A clinical commissioning policy is intended to replace this interim position statement.

Factors for decision making

Effectiveness and safety

Evidence was from 4 published randomised controlled trials (RCTs) in adults hospitalised with COVID-19 pneumonia (Salama et al. 2021 [EMPACTA], Salvarini et al. 2021 [RCT-TCZ-COVID-19], Stone et al. 2020 [BACC Bay Tocilizumab Trial], Hermine et al. 2020 [CORIMUNO-TOCI]) and pre-publication study results from REMAP-CAP (study NCT02735707), a nationally prioritised platform study in adults.

In REMAP-CAP (n=778), patients had severe COVID-19, were critically ill in an intensive care setting, and 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. (2020) (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.

Tocilizumab was given intravenously at an initial dose of 8 mg/kg in all the studies (up to a maximum of 800 mg). In Stone et al. (2020) only this single dose was given. In Salvaraini et al. (2021) all patients had a second dose after 12 hours. In the other studies, an additional dose could be given after 8 to 24 hours (this varied between the studies) if needed. The standard care treatments used

in the studies varied but all included corticosteroids in varying proportions of use. In REMAP-CAP, corticosteroids were used in most patients and remdesivir in about a third of patients.

In REMAP-CAP, 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 3 RCTs in adults with severe COVID-19 who were not ventilated at baseline were mixed. In Salama et al. (2020), 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) and Stone et al. (2020) there were no statistically significant differences in death, or in combined outcomes of death, mechanical ventilation or intensive care admission, with tocilizumab compared with placebo or standard care. These 3 RCTs also found no statistically significant differences between tocilizumab and placebo or standard care in time to hospital discharge, time to improvement (or worsening) in clinical status, or clinical worsening.

In the RCT of adults with moderate to severe COVID-19 who were not ventilated at baseline (Hermine et al. 2021), there were no statistically significant differences between tocilizumab and standard care in the combined outcomes of non-invasive ventilation, mechanical ventilation or death, or in clinical status.

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

Stone et al. (2020) and Salama et al. (2020) found no statistically significant difference between tocilizumab and standard care in age, sex, ethnicity, obesity, diabetes, and concomitant treatment subgroup analyses. In the unpublished study results from REMAP-CAP there was insufficient detail to accurately assess subgroups of interest.

Limitations of the evidence

REMAP-CAP was the only study to investigate people who were critically ill with severe COVID-19 receiving organ support in an intensive care setting. In this study, patients had to be enrolled within 24 hours of starting organ support. Hermine et al (2021) included people with moderate to severe COVID-19, and all other studies (Salama et al 2020, Salvarani et al. 2021, and Stone et al. 2020) included people with severe COVID-19. The definition of severe COVID-19 differed between these studies, but all RCTs apart from REMAP-CAP excluded people receiving non-invasive or mechanical ventilation.

Risk of bias was rated as either 'some concerns' or 'low' for all the studies. Hermine et al (2021), REMAP-CAP, and Salvarani et al (2021) were open-label studies. REMAP-CAP (study NCT02735707) is a nationally prioritised platform study, but the data were preliminary and unpublished. The study results have not been peer reviewed, and there was insufficient detail available to accurately assess the statistical approach taken. RECOVERY (study NCT04381936), another nationally prioritised platform study investigating tocilizumab in hospitalised patients with COVID-19 is ongoing. Results of this will add to the evidence base for tocilizumab for COVID-19.

The published studies had relatively small patient numbers. Most had a 1-month follow-up period for the primary outcomes, and some patients were still in hospital at the time of publication. Therefore, the long-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.

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