Clinical Guideline
Tocilizumab for patients admitted to ICU with COVID-19 pneumonia (adults)

Overview

Tocilizumab is a recombinant humanised monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts [4]. In COVID-19, tocilizumab may mitigate the cytokine release syndrome and prevent progression in severe disease. Currently, tocilizumab is licensed for the use of rheumatoid arthritis, juvenile idiopathic polyarthritis, giant cell arteritis and cytokine release syndrome [1,2,3, 4].

Tocilizumab use in COVID-19 is OFF-LABEL.

Eligibility criteria

Patients have been admitted to ICU with severe pneumonia requiring respiratory support, such as high-flow nasal oxygen, non-invasive ventilation, or invasive mechanical ventilation; and with COVID-19 infection that is confirmed by microbiological testing or where staff are confident that COVID-19 is the most likely diagnosis based on clinical and radiological features [1,2,3].

Exclusion criteria [1,2,3]

- Previously treated with other IL-6 inhibitors, such as sarilumab within the current admission
- Hypersensitivity to tocilizumab
- Co-existing infection that might be worsened by tocilizumab
- It's been more than 24 hours since ICU admission or more than 24 hours after starting respiratory support
- Pre-existing condition or treatment resulting in ongoing immunosuppression
- Baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 5 times the upper limit of normal (ULN)
- Baseline absolute neutrophil count (ANC) below 2 x 10^9/L
- Baseline platelet count below 50 x 10^9/L

Caution [1, 4]

- Patients with latent tuberculosis should be treated with standard therapy before starting tocilizumab
- Patients with ALT or AST more than 1.5 times the ULN
- Patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes and interstitial lung disease) which may predispose patients to infections.
- Patients with platelet count below 100 x 10^9/ L)
- Viral activation (e.g. Hepatitis B) has been reported with biologic therapies
- Live and live attenuated vaccines should not be given concurrently with tocilizumab as clinical safety has not been established
- Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with tocilizumab is currently unknown.

A full list of caution can be found on:
https://www.medicines.org.uk/emc/product/6673/smpc

Stopping criteria [1,3, 4]

Patients who develop:

- an ANC < 0.5 x 10^9/ L or a platelet count < 50 x 10^9/L
- ALT or AST more than 5 times the ULN
- an anaphylactic reaction or other serious hypersensitivity / serious infusion related reaction

Dose and method of administration

The recommended dose of tocilizumab is 8 mg/kg body weight (up to a maximum dose of 800mg) for a single dose. A second dose should not be considered [8]

NHS England [2] recommends the following dose bandings:

Weight	Dose
<41kg	8mg/kg (round to 20mg)
41-45kg	360mg
46-55kg	400mg
56-65kg	480mg
66-80kg	600mg
81-90kg	680mg
>91kg	800mg

Tocilizumab is given as an intravenous infusion over 60 minutes in a 100mL sodium chloride 0.9% infusion bag. Tocilizumab should not be infused concomitantly in the same IV line with other medications[4, 5, 6].

Method of administration can be found on Medusa: https://injmed.wales.nhs.uk/ or via SharePoint.

Tocilizumab is a monoclonal antibody and so reduce direct handling to a minimum and wear appropriate personal protective equipment. Patients can develop hypersensitivity reactions, therefore monitor for anaphylaxis signs such as flushing, fever, chills, rash, pruritus, urticaria, headache and hypertension. The patient's pulse, blood pressure, temperature & respiration rate should be measured after 15 minutes, then every 30 minutes until 1-hour post infusion [6].

Adverse drug effects

The most commonly reported ADRs were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT. The most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions [4]. Any suspected ADRs for patients receiving tocilizumab should be reported directly to the MHRA via the new dedicated COVID-19 yellow card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/

Pregnancy and breastfeeding

Women of childbearing potential must use effective contraception during and up to 3 months after treatment. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose, the potential risk for humans is unknown so the use of tocilizumab should not be used during pregnancy unless clearly necessary.
The excretion of tocilizumab in milk has not been studied in animals. The decision on whether to continue/ discontinue breastfeeding or treatment should be made based on the benefit of breastfeeding and the benefit of patient [3, 4].

Co-administration

There is no interaction of tocilizumab with dexamethasone/ hydrocortisone or remdesivir [1, 4].

For further information on interactions, please visit the university of Liverpool covid-19 drug interactions website: https://www.covid19-druginteractions.org/

Ongoing Monitoring

Patients who have been treated with tocilizumab should be given an information leaflet and advised to report any signs of infection. The infection risk remains for approximately 3 months after the last dose. The Information leaflet is available at https://www.sps.nhs.uk/wp-content/uploads/2021/03/COVID-19-Patient-Discharge-Information-Leaflet-Tocilizumab-Sarilumab.pdf
This information should also be shared with the patient's GP, who should be made aware of the infection risk and escalate if appropriate.

References

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8. NHS England. COVID-19 Interim Clinical Commissioning Policy : IL-6 inhibitors (tocilizumab or sarilumab) for hospitalised patients with COVID-19 (adults) [Accessed 29th September 2021] Available from : www.downloads/Interim%20Clinical%20Commissioning%20Policy%20(2).pdf