USE OF TOCILIZUMAB FOR COVID-19 IN HOSPITALISED ADULTS DRUG GUIDELINE

Tocilizumab (Actemra®) is registered for use in Australia for the treatment of arthritis, giant cell arteritis and cytokine release syndrome but not for the treatment of COVID-19. In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the National Taskforce (25/2/21) gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).[1,2]

This guideline requires endorsement by your local Drug and Therapeutics Committee prior to implementation.

Supply of tocilizumab for registered indications and clinical trials takes precedence over supply for off-label use outside of clinical trials.

This guideline aims to provide supportive information for clinicians if they decide to prescribe tocilizumab for off-label use in hospitalised patients with COVID-19 when patients are not eligible for a clinical trial or when a clinical trial is not available.[2] *This guideline should be used in conjunction with an Individual Patient Use (IPU) application form, outcomes reporting form, patient consent form and patient information leaflet - link. Off-label use of tocilizumab is not recommended in the Hospital in the Home setting or in community-based patients with COVID-19.*

*This guidance does **not** apply to use in children. The standard of care in children is supportive therapy. Any experimental use of immunomodulation therapy for COVID-19 in children should include expert advice from a paediatrician, infectious diseases specialist and immunologist and follow the local governance processes.*

Drug Class: Anti-rheumatic, cytokine modulator, monoclonal antibody (humanised).[3]

Authorised Prescribers:

- Immunologists,
- Infectious disease physicians,
- Intensivists,
- Haematologists, and
- Respiratory physicians.

Indication for applying this guidance[1]:

At the treating clinician's discretion, in consultation with a second opinion from a specialist in the field of respiratory medicine, intensive care, infectious diseases, immunology[#] or haematology and in accordance with relevant Drug and Therapeutics Committee approval, off-label tocilizumab may be considered for:

- patients with a current diagnosis of COVID-19, who require supplemental oxygen, particularly where there is evidence of systemic inflammation.[1]

Markers of systemic inflammation include elevated ESR, C-reactive protein (CRP), D-dimers, lactate dehydrogenase, ferritin, and increased concentrations of proinflammatory cytokines including IL-1 and IL-6. In the largest trial on the treatment of tocilizumab, the criterion for systemic inflammation was defined as CRP ≥75 mg/L.[4] However, as tocilizumab inhibits the production of CRP, a reduction in CRP should not be used as a marker of clinical improvement.

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit of using corticosteroids in conjunction with tocilizumab. Use of combined tocilizumab and corticosteroids should be considered in patients hospitalised with COVID-19 who require oxygen; however the optimal sequencing of tocilizumab and corticosteroids is unclear.[1,5]

Contraindications and Precautions[3,5-8]:

- Contraindicated in patients with a history of any reaction consistent with hypersensitivity to any component of the product, Chinese hamster ovary cell products or other recombinant human or humanised antibodies[†]. Exercise caution in patients with a history of anaphylaxis to other medicines.
- Contraindicated in sepsis or active, severe infections from non-COVID-19 pathogens[8]. Serious and sometimes fatal infections (including tuberculosis reactivation, opportunistic infections) have been reported in patients receiving immunosuppressive agents including tocilizumab.
- Clinicians should exercise caution when considering the use of tocilizumab in patients with[5]:
  - A history of recurring or chronic infection, or with underlying conditions (e.g. diabetes) which may predispose patients to infections.
  - A history of HIV, positive core antibody for hepatitis B, prior HCV infection or symptomatic EBV infection
  - A history of tuberculosis/tuberculosis exposure
  - Concurrent immunosuppressive/anti-rejection therapy, increases the risk of infection and should be avoided.

  N.B. Baseline testing for hepatitis B, HCV and tuberculosis should be undertaken. Tocilizumab treatment should NOT be delayed pending results of baseline tests.
- Live and live-attenuated vaccines should not be given concurrently (see below).
- In patients with haematological abnormalities including the possibility of macrophage activation syndrome (MAS) or haemophagocytic lymphohistiocytosis, advice from a haematologist should be sought especially in those with[3,6]:
  - Absolute neutrophil count <2 x 10^9/L
  - Platelets <100 x 10^9/L

[#] If a hospital has no immunologist, the Australasian Society of Clinical Immunology and Allergy (ASCIA) can provide contact details of an Immunologist who will help provide advice and consultation within NSW or Australia

[†] For further information & examples see: Medicines/pharmaceuticals of animal origin

- Exercise caution in patients with active hepatic disease or hepatic impairment including abnormal liver enzymes (transaminases 3–5 times the upper limit of normal).[5,7]
- Use with caution in patients with current or previous history of diverticulitis or intestinal ulceration.
- Tocilizumab is a Category C medication. Recommendations for use in pregnant or breastfeeding women are evolving. See National COVID-19 Clinical Evidence Taskforce guidelines.

Drug Interactions[3,9,10]:

Potential drug interactions have not been investigated in patients with COVID-19. Consider:

- Tocilizumab has no inhibitory or inducing effects on cytochromes. However, patients with COVID-19 may experience an elevation of IL-6, which has been shown to suppress activity of drug metabolising enzymes, namely CYP3A4, but also others. Tocilizumab will normalise cytochrome activity (via inhibition of IL-6).
- The indirect effect of tocilizumab on CYP450 enzyme activity in this setting is unknown but the effects may persist for several weeks after administration.
- The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (further information).
- Caution should be exercised when using CYP3A4 substrates, especially where reduced effectiveness is undesirable. Specific CYP3A4 substrates possibly being co-prescribed include benzodiazepines.
- Specialist input should be obtained regarding timing of future vaccinations. Live and live-attenuated vaccines should be avoided for 6 months. Information is likely to evolve. Refer to Centre for Disease Control and Prevention (CDC) and Australian Immunisation Handbook for further information or contact the NSW Immunisation Specialist Service (NSWISS) Advice Line (1800 679 477).

A variety of resources are available to check specific drug combinations, e.g. Liverpool COVID-19 Drug Interactions tool. Contact the local pharmacy department or medicines information service for tailored advice.

Dose[1,8,11]:

The suggested dose is dependent on body weight:

Weight	Dose
Patients >90 kg	800 mg
Patients >65 and ≤90 kg	600 mg
Patients >40 and ≤65 kg	400 mg
Patients ≤40 kg	8 mg/kg

Administer as **a single intravenous infusion over 60 minutes**, with the potential for a second dose to be administered either 12 or 24 hours later if the patient's condition has not improved.

Presentation and storage[3]:

Available as:

- 80 mg/4 mL concentrate solution for IV infusion vial (≈$86/vial)
- 200 mg/10 mL concentrate solution for IV Infusion vial (≈$212/vial)
- 400 mg/20 mL concentrate solution for IV Infusion vial (≈$422/vial)

Store vials at 2–8°C. (Refrigerate. Do not freeze.)

Preparation and administration[3,11]:

- The occupational hazard of intermittent low dose exposure to tocilizumab is not known. Wear a mask and gloves when preparing the infusion solution to minimise exposure.
- If made at the bedside, administer infusion immediately after preparation and discard remaining vials. If made in an aseptic environment, the diluted solution may be stored at 2–8°C for 24 hours prior to administration.

Steps
1. Ascertain the volume of tocilizumab solution that will be required. Withdraw this same volume from a 100 mL sodium chloride 0.9% infusion bag. 2. Withdraw the tocilizumab dose from the vial(s) & add to the sodium chloride 0.9% infusion bag. 3. Invert gently when mixing to avoid foaming. Do NOT shake. Inspect the bag, which must be clear to opalescent, colourless to pale yellow and free from visible particles. 4. Do not use the same IV line to administer other medications at the same time. 5. Prime the line with tocilizumab infusion and then infuse intravenously over 60 minutes via a central or peripheral line. 6. The infusion rate must be 10 mL per hour for 15 minutes and then may be increased to 130 mL per hour for the next 45 minutes. 7. After completion of the tocilizumab infusion, at least 20 mL of 0.9% sodium chloride should be used to flush the giving set (at the same rate as the final tocilizumab infusion).

Monitoring Requirements[3,11,12]:

- Monitor for adverse effects (as below) – including FBC, LFTs, new onset GIT symptoms.
- Observe for hypersensitivity reaction during, and for 30 minutes after, each IV infusion. Resuscitation facilities must be readily available.

Adverse Effects[¥ 3,6,12,13]:

It may be difficult to distinguish between adverse effects of tocilizumab and signs and symptoms of COVID-19. As the proposed use is off-label, it is important to document and report all (from possible to confirmed) adverse effects experienced by the patient during treatment to inform its safety profile and future use. ¥ Refer to product information for complete list of possible adverse effects.

- **Common (>1%):**
  Infections (including opportunistic), neutropenia, hypofibrinogenaemia, increased liver enzymes, gastritis, mouth ulcers, hypertension, infusion-related reactions (below), antibodies to tocilizumab, rash, itch, headache, dizziness.
- **Infrequent (0.1–1%):**
  GI perforation (possibly dose-related), thrombocytopenia, hypersensitivity reactions (e.g. urticaria, angioedema), dyspnoea, cough, conjunctivitis.
- **Rare (<0.1%):**
  Serious hepatotoxicity (including acute liver failure, hepatitis and jaundice, in some rare cases treatment has required liver transplant), pancreatitis, pulmonary fibrosis.

Infusion-related reactions: Occur within 24 hours of IV infusion; they include hypertension, headache, rash, hypersensitivity (anaphylaxis 0.2%).

Reporting:

Access via the IPU pathway will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicines use. The prescribing clinician is responsible for reporting medication errors and adverse events occurring as a result of tocilizumab treatment:

- Adverse events related to medicines should be reported to the TGA and via the hospital ims+ or Riskman system.
- Approval of off-label tocilizumab IPU requires reporting of clinical outcomes. IPU applications and outcome reporting should occur as per local governance processes. A NSW TAG-developed drug registry using online IPU application and outcome reporting processes has been developed. See http://www.nswtag.org.au/resources-for-experimental-medicines-for-the-treatment-of-covid-19/. Contact your local DTC or pharmacist for further information.

References:

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