EXPERIMENTAL USE OF TOCILIZUMAB FOR SEVERE 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 infection. Evidence from case series in patients with severe or critical COVID-19 pneumonia suggests possible benefit from immunomodulators, such as tocilizumab. The safety of this approach is unclear.

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 experimental off label use outside of clinical trials.

This guideline aims to provide supportive information for clinicians if they decide to prescribe tocilizumab for experimental, off-label use in hospitalised patients with a COVID-19 infection, when patients are not eligible for a clinical trial or when a clinical trial is not available. This guideline should be used in conjunction with an Individual Patient Use (IPU) application form, patient consent form and patient information leaflet - link. Off-label experimental 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. There are currently no trials in Australia open to children and young people < 18 years of age. 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) [1]

Presentation:

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)

If there are shortages of concentrate solutions for IV infusion, the 162 mg/0.9 mL solution for subcutaneous injection at a dose of 324 mg (2 x 162mg) subcutaneously may be considered. [2]
Store at 2°C – 8°C.

Authorised Prescribers:

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

Indication for applying this guidance:

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, experimental, off-label tocilizumab may be considered for:

- patients with a current diagnosis of SARS-CoV-2, who have severe or critical illness and are clinically deteriorating [(3)], despite receiving standard care, and are considered by the treating and consulting clinicians to have a high risk of mortality. Markers of an exaggerated inflammatory response are supportive features in favour of tocilizumab use e.g. D-dimer level > 1 mg/L, CRP level ≥ 100 mg/L, ferritin level >750 microg/L or IL-6 > 100 pg/mL.[(10)]

Contraindications and Precautions: [(1; 4; 5; 6)]

- Hypersensitivity including anaphylaxis: 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. (Reported to occur in approximately 1.5% of rheumatoid arthritis patients receiving tocilizumab).
- Sepsis or infections from non-COVID-19 pathogen. 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 a history of:
  - Recurring or chronic infection, or with underlying conditions (e.g. diabetes) which may predispose patients to infections.
  - HIV, positive core antibody for hepatitis B, prior HCV infection, or symptomatic EBV infection
  - 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.
- In patients with haematological abnormalities including concerns around macrophage activation syndrome (MAS) or haemophagocytic lymphohistiocytosis, advice from a haematologist should be sought especially in those with: [(1; 4)]
  - Absolute neutrophil count < 2 x 10^9/L
  - Platelets < 100 x 10^9/L
- Active hepatic disease and hepatic impairment including abnormal liver enzymes transaminases 3-5 times the upper limit of normal [(6)]
- A history of active diverticulitis is a contraindication due to risk of GI perforation.
- Use with caution in patients with previous history of intestinal ulceration.
- Tocilizumab is a Category C medication and not recommended in pregnancy or breastfeeding, although the maternal and foetal risks should be considered in the context of the severity of SARS-CoV-2 CRS and critical illness. Women of childbearing potential should be advised to use adequate contraception for several months after treatment.

[#] 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

Drug Interactions: [1; 12] , [14]

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

- Tocilizumab has no inhibitory or inducing effects on cytochromes. However, patients infected 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 ritonavir/lopinavir and benzodiazepines.
- Specialist input should be obtained regarding timing of future vaccinations.

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: [2; 4; 5; 7; 8; 9; 10; 11]

Optimal dosing and duration of treatment is unknown. The suggested dose and duration (which may be updated as data from clinical trials becomes available) is:

8 mg/kg (maximum 800 mg); round dose to the nearest 10mg.

Dose may be repeated after 8-12 hours, if symptoms worsen or show no improvement.
If considering more than 2 doses, seek further specialist advice. [11]

Preparation and administration: [7]

- 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 2-8C for 24 hours prior to administration.
- Ascertain the volume of tocilizumab solution that will be required. Withdraw this same volume from a 100 mL sodium chloride 0.9% infusion bag.
- Withdraw the tocilizumab dose from the vial(s) & add to the sodium chloride 0.9% infusion bag.
- 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.
- Do not use the same IV line to administer other medications at the same time.
- Prime the line with tocilizumab infusion and then infuse intravenously over 60 minutes via a central or peripheral line.
- The infusion rate must be 10 mL per hour for 15 minutes and then increased to 130 mL per hour for the next 45 minutes.
- 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 tocilizumab infusion).

Monitoring Requirements: [1]

- 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¥: [4; 13]

It may be difficult to distinguish tocilizumab's adverse effects and signs and symptoms of COVID-19 infection. As the proposed use is experimental, it is important to document and report all adverse effects (from possible to confirmed) 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).

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 in the hospital IIMS+ or Riskman system
- Approval of experimental, 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 is in development. See http://www.nswtag.org.au/resources-for-experimental-medicines-for-the-treatment-of-covid-19/

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