Interleukin-6 Receptor Antagonists for adult patients with COVID pneumonia

Guidance for use in GGC

Tocilizumab was licensed in December 2021 for the treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. This places tocilizumab as the first-line IL-6 inhibitor for hospitalised patients with COVID-19. Patients may continue to be considered for treatment with sarilumab where tocilizumab is unavailable for this indication or cannot be used.

The REMAP-CAP trial reported a finding of survival and time to recovery benefits for Interleukin-6 Receptor Antagonists (IL6RAs) tocilizumab or sarilumab, over and above current standard of care (including corticosteroids), in the immune modulation therapy domain of the REMAP-CAP platform trial. Mortality was reported as 35.8% in the placebo group, compared to 27% in the treatment group, an overall reduction in the risk of death of 24%. The treatment also reduced the requirement for invasive mechanical ventilation and the duration of critical care stay by more than a week on average. In addition, the RECOVERY trial has now reported a survival benefit with tocilizumab in hospitalised COVID-19 patients with hypoxia and systemic inflammation. These benefits were seen regardless of the level of respiratory support and were additional to the benefits of systemic steroids, such as dexamethasone.

A prospective meta-analysis of clinical trials of IL-6 inhibitors in patients hospitalized for COVID-19 showed that they were associated with lower 28-day all-cause mortality. These results led to a strong recommendation for the use of both IL-6 inhibitors (tocilizumab and sarilumab) to treat severe and critical COVID-19 in the World Health Organization (WHO) Therapeutics and COVID-19 Living Guideline. The guideline, which was updated in July 2021 and further updated in September 2022, did not recommend the use of one IL-6 inhibitor over the other. The NICE Rapid Guideline on managing COVID-19 (last updated July 2022) currently recommends the use of sarilumab for adults in hospital with COVID-19 if tocilizumab cannot be used or is unavailable.

Eligibility criteria

The decision to treat with an IL6RA is not an emergency and should be made judiciously after assessment and in a timely manner during office hours. **Discussion with a named consultant familiar with the management of COVID pneumonitis during working hours must be documented**.

Patients are eligible to be considered for **tocilizumab** or sarilumab where:

- COVID-19 infection is confirmed by virological testing or where a multidisciplinary team has a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis;

  AND
- They are receiving (or have completed a course of) dexamethasone or an equivalent corticosteroid unless contraindicated.
- **AND**, either one of the following:
  - they have a C-reactive protein level of at least 75mg/L; AND a SpO_2 <92% on room air or requirement for supplemental oxygen; **OR**

- They are within 48 hours of starting respiratory support for COVID pneumonia (high-flow nasal oxygen, continuous positive airway pressure (CPAP), non-invasive ventilation, invasive mechanical ventilation),regardless of C-reactive protein level..

- **AND** not already treated during this episode with an IL-6 inhibitor.

Choice of drug:
Tocilizumab should be used as the first choice whenever possible, but either agent can be used for the treatment of severe and critical COVID 19 in all ward settings. At times of low/restricted stock of either agent one may be advised locally for use in preference to the other. Tocilizumab is the IL6 Inhibitor treatment of choice for pregnant patients and should be reserved for this patient group at times of low/restricted stock. The use of sarilumab intravenously in COVID-19 is offlabel

Exclusion criteria

Tocilizumab or sarilumab should not be administered in the following circumstances:

- COVID-19 hospital admission >21 days
- Known hypersensitivity to tocilizumab or sarilumab
- Co-existing **severe** infection that might be worsened by tocilizumab or sarilumab
    - Any active, severe infection other than COVID-19 causing physiological derangement.

Tocilizumab should not be administered in the following circumstance:

- An alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 10 times the upper limit of normal
- A neutrophil count of less than 1 x 10^9/L
- A platelet count of less than 50 x 10^9/L

Sarilumab should not be administered in the following circumstance:

- baseline platelet count of less than 150 x 10^9/L
- An alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 5 times the upper limit of normal
- Absolute neutrophil count of less than 2 x 10^9/L

Clinical criteria requiring further consideration and caution

Tocilizumab or sarilumab should be used with caution in the following circumstances:

- Caution is advised when considering the use of tocilizumab or sarilumab in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections.
- A pre-existing condition or treatment resulting in ongoing immunosuppression
- Caution is recommended if hepatic enzymes are more than 1.5 times the upper limit of normal.

- Caution is also necessary when prescribing IL-6 inhibitors to patients with neutropenia or thrombocytopenia. Please note that C-reactive protein (CRP) levels may be depressed for some time after treatment with tocilizumab

Pregnancy and women of childbearing potential

The REMAP-CAP trial excluded pregnant women, whereas the RECOVERY trial (recruitment ongoing) has included pregnant women. The SmPC for sarilumab and tocilizumab currently states: "Women of childbearing potential must use effective contraception during and up to 3 months after treatment." In relation to use in pregnancy, the SmPC for tocilizumab states "there is no adequate data for the use in pregnant women. A study in animals has shown an increased risk of spontaneous abortion/embryo-foetal death at a high dose with tocilizumab." In relation to use in pregnancy, the SmPC for sarilumab states "There are no or limited amount of data from the use of sarilumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity".

Both SmPCs for tocilizumab and sarilumab state that they should only be used during pregnancy when clinically necessary at the discretion of the treating clinician.

The Royal College of Obstetrician and Gynaecologists advise to strongly consider the use of tocilizumab for the treatment of pregnant patients if C-reactive protein at or above 75 mg/l or in ICU. It is recommended that any decision to treat with anti-IL6 agents should be taken by an MDT, including obstetric and infection specialists, and given if the benefits outweigh the risks.

Tocilizumab is the IL6 inhibitor of choice for the treatment of COVID-19 in pregnant patents, whenever possible. However, if there is no stock available, sarilumab may be used.

Administration:

Before prescribing, patients must fulfil the criteria defined above and have approval from a Consultant familiar with the management of COVID pneumonitis (contacted in daytime hours as the administration of an IL6RA is not an emergency.) HDU/ICU areas will keep a stock of tocilizumab/sarilumab (see table below for local arrangements). For other ward areas tocilizumab/sarilumab should be obtained from pharmacy (if pharmacy is closed a supply can obtained from locations below). **Please do not contact the on-call pharmacist out of hours for supply.** If using ICU/HDU stock patient details MUST be recorded in the appropriate Controlled Drugs register. Tocilizumab and sarilumab must be stored in a fridge when not in use. Both must be stored in original cartons to protect from light.

Drug	GRI	QEUH	RAH	Inverclyde
Tocilizumab	C19HDU (Fridge in non AGP area)	HDU 7	HDU	HDU/CCU (J Centre)
Sarilumab	C19HDU ICU West	HDU 7 ICU-2	HDU ICU-1	HDU/CCU (J Centre)

Tocilizumab dosing

Tocilizumab is administered as an intravenous infusion at a dose of 8mg per kg, up to a maximum dose of 800mg. The following dose bandings are suggested:

Weight	**Dose**
<41kg	8mg/kg, rounded to nearest 20mg
≥ 41kg and ≤ 45kg	360mg
≥ 46kg and ≤ 55kg	400mg
≥ 56kg and ≤ 65kg	480mg
≥ 66kg and ≤ 80kg	600mg
≥ 81kg and ≤ 90kg	680mg
≥91kg	800mg

Tocilizumab must be diluted in a 100mL bag of 0.9% sodium chloride, after removing an equivalent volume of saline (total volume 100mL) and given over 1 hour.

- Infuse at 10 mL/hour for 15 minutes followed by 130 mL/hour for 45 minutes to complete dosing over 1 hour)
- Ensure that the infusion bag is emptied, flushing any remaining solution through the intravenous tubing set with 20 mL of normal saline (or the volume needed to flush the entire tubing if different than 20 mL) following standard procedures.
- **Tocilizumab should not be infused concomitantly in the same IV line with other medications.**

A single dose is to be administered within 24 hours of meeting the eligibility criteria or as soon as possible thereafter. It is anticipated that this will occur during daytime hours. A second dose should not be considered, given the uncertainty over evidence of additional benefit as well as the need to maximise available supply. Ensure monitoring of LFTs and FBC in the 72 hours following administration as tocilizumab can lead to transaminitis, neutropenia and thrombocytopenia.

Sarilumab dosing

The recommended dose of sarilumab is 400mg to be delivered as a once-only intravenous infusion. Sarilumab is available as a pre-filled syringe. Two 200mg doses should be used to make up the total 400mg dose. 400mg of sarilumab must be diluted in a 100mL bag of 0.9% sodium chloride, and given over 1 hour, via 0.2 micron inline filter.

- Infuse at 10 mL/hour for 15 minutes followed by 130 mL/hour for 45 minutes to complete dosing over 1 hour)
- Ensure that the infusion bag is emptied, flushing any remaining solution through the intravenous tubing set with 20 mL of normal saline (or the volume needed to flush the entire tubing if different than 20 mL) following standard procedures.
- **Sarilumab should not be infused concomitantly in the same IV line with other medications.**

Combination Treatment

IL-6 inhibitors may be administered in combination with baricitinib (as well as corticosteroids, unless contraindicated), according to clinical judgement, in patients with severe or critical COVID-19. The WHO makes a strong recommendation for IL-6 inhibitors in all patients with severe/critical COVID-19, and also states that they may be co-administered with baricitinib and corticosteroids. (WHO, September 2022).

Co-administration

There is no interaction expected between IL-6 inhibitors with other commissioned COVID-19 treatments. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Caution

Both tocilizumab and sarilumab are potent immunosuppressant drugs. Patients are at risk of opportunistic infection following administration. Both drugs will suppress neutrophil count and C-reactive protein for up to 1 month and these should not be relied upon as indicators of infection/ inflammation.

Regarding the neutropenia, there is an immediate reduction in circulating neutrophils following IL6RAs administration likely due to margination and/or bone marrow trafficking. This however doesn't affect neutrophil function, i.e. they do not need to be treated like 'true' neutropenic patients, and are not at risk of neutropenic sepsis.

There is a small risk of a viral hepatitis flare or re-activation in patients with chronic viral hepatitis following IL6RA administration. Please consider HBV/HCV testing in patients who develop a transaminitis after treatment.

All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) should explicitly mention that an IL-6 inhibitor has been given and the date of administration.

COVID-19
CLINICAL GUIDELINE

Note: This guideline has been fast-tracked for approval for use within NHSGGC

Covid-19 Interleukin-6 Receptor Antagonists for adult patients with COVID pneumonia

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.