Interleukin-6 Receptor Antagonists for adult patients with COVID pneumonia

Guidance for use in GGC

The REMAP-CAP trial has 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.

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** 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:
  - With a C-reactive protein level of at least 75mg/L; AND a SpO_2 <92% on room air or requirement for supplemental oxygen; OR
  - Within 24-48 hours of starting respiratory support for COVID pneumonia (high-flow nasal oxygen, continuous positive airway pressure (CPAP), non-invasive ventilation, invasive mechanical ventilation).
- AND not already treated during this episode with an IL-6 inhibitor.

Patients are eligible to be considered for **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
- Within 24-48 hours of starting respiratory support for COVID pneumonia (high-flow nasal oxygen, continuous positive airway pressure (CPAP), non-invasive ventilation, invasive mechanical ventilation),
- AND not already treated during this episode with an IL-6 inhibitor.

Choice of drug:
Tocilizumab is the agent of choice in ward settings. Where patients are admitted to ICU, sarilumab can be used as an alternative IL-6 receptor antagonist.

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.

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
- A platelet count of less than 50 x 109/L
- A neutrophil count of less than 2 x 109/L
- An alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 5 times the upper limit of normal (caution is recommended if hepatic enzymes are more than 1.5 times the upper limit of normal)

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. Tocilizumab or sarilumab should only be used during pregnancy when clinically necessary at the discretion of the treating clinician.

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 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	ICU West	ICU-2	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.**

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.