IL-6 inhibitors (tocilizumab or sarilumab) for COVID 19 pneumonitis in adults and postpubescent children

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Trust Ref: B34/2021

1. Introduction

Tocilizumab and sarilumab are humanised monoclonal antibodies against the IL-6 receptor which block the activity of pro-inflammatory cytokines.

Tocilizumab has a marketing authorisation for use in the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. Tocilizumab for intravenous use also has a marketing authorisation for the treatment of moderate to severe rheumatoid arthritis and the treatment of active systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis and CAR-T induced cytokine release syndrome (CRS).

Sarilumab (Kevzara) for subcutaneous use has a marketing authorisation for moderate to severe rheumatoid arthritis. Use of sarilumab under this policy as a treatment for COVID-19 is off-label.

Evidence from the REMAP-CAP trial demonstrates a clinical benefit with the use of tocilizumab or sarilumab in patients with COVID-19 requiring organ support. In February 2021, the RECOVERY trial announced the findings of tocilizumab use in a broader hospitalised population, which indicated that tocilizumab significantly improved survival and other clinical outcomes in patients with hypoxaemia and systemic inflammation (severe COVID-19).

New evidence and guidance have since emerged to indicate the possibility of equivalence between the two IL-6 inhibitors, which is summarised below:

- Further evidence from the REMAP-CAP trial has demonstrated equivalent effects of both IL-6 inhibitors on survival and requirement for organ support (84.9% posterior probability of equivalence).
- 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.

2. Scope

This guideline outlines patient eligibility for IL-6 inhibitors, the prescribing and review requirements, and the procedure to obtain IL-6 inhibitors for UHL patients that are hospitalised **due to** symptoms of COVID-19.

This guideline applies to all UHL staff involved in the prescribing and administration of IL-6 inhibitors for adult and postpubescent children with COVID-19.

3. Recommendations, Standards and Procedural Statements

3.1 Patient selection

Patients are eligible for treatment with an IL-6 inhibitor if they meet ALL of the following criteria:

1. COVID-19 infection confirmed by microbiological testing or where the MDT agree that there is a high level of confidence that COVID-19 is most likely diagnosis.

2. Receiving dexamethasone or an equivalent corticosteroid unless contraindicated.

3. Commenced respiratory support (high-flow oxygen, CPAP, NIV or invasive ventilation) for COVID-19 pneumonitis within the last 48 hours, regardless of C-reactive protein level.

OR

With a C-reactive protein level of at least 75mg/L; AND an oxygen saturation of <92% on room air OR requirement for supplemental oxygen

4. Decision to initiate treatment with an IL-6 inhibitor should be made by the receiving consultant and with the support from multi-disciplinary colleagues in cases of uncertainty.

3.2 Exclusion criteria

- Previous treatment with another IL-6 inhibitor during this episode

Tocilizumab should not be administered in the following circumstances:

- Known hypersensitivity to tocilizumab
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than ten times the upper limit of normal
- A pre-treatment platelet count of less than 50 x 10^9/L
- A pre-treatment absolute neutrophil count of less than 1 x 10^9/L

Sarilumab should not be administered in the following circumstances:

- Known hypersensitivity to sarilumab
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than five times the upper limit of normal
- A pre-treatment platelet count of less than 150 x 10^9/L
- A pre-treatment absolute neutrophil count of less than 2 x 10^9/L

3.3 Cautions

- A pre-existing condition or treatment resulting in ongoing immunosuppression.
- Patient death imminent in the next 24 hours or continuation of life sustaining treatment not felt to be in patient's interests by senior clinician/ patient with mental capacity
- Co-existing active untreated bacterial/ fungal infection that might be worsened by IL-6 inhibitor therapy.
- Thrombocytopaenia with platelets between 50 to 150 x10^9/L for tocilizumab.
- Neutropaenia. Please note that C-reactive protein (CRP) levels may be depressed for some time after treatment with tocilizumab or sarilumab.

Please refer to the Summary of Product Characteristics (SmPC) for tocilizumab and sarilumab for special warnings and precautions for use, although some may not be relevant for use in the acute setting, as the historical licensed indications address long-term use.

3.4 Pregnancy and women of childbearing potential

Tocilizumab and sarilumab should not be used during pregnancy unless clinically necessary and must always be discussed with the on-call gynaecologist or obstetrician.

The SmPC for tocilizumab currently states that: *"Women of childbearing potential must use effective contraception during and up to 3 months after treatment. There are no adequate data from the use of tocilizumab in pregnant women. 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. RoActemra should not be used during pregnancy unless clearly necessary."*

The SmPC for sarilumab currently states that: *"Women of childbearing potential should use effective contraception during and up to 3 months after treatment. 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. Kevzara should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab."*

The SmPC for tocilizumab and sarilumab should be consulted if further information is required.

3.5 Breastfeeding

Tocilizumab and sarilumab are very large molecules, so it will be very difficult for them to pass into breast milk.

As both have negligible oral bioavailability, and is are protein molecules that will be mostly destroyed in the infant's gastrointestinal tract, infant absorption via breast milk would be insignificant. Absorption may be increased slightly in the neonatal period due to increased gastrointestinal permeability, although this has not been proven.

SPS advice on using IL-6 inhibitors in hospitalised patients with COVID-19 who are breastfeeding should be consulted if further information is required.

3.6 Blueteq prior registration

All prescriptions for tocilizumab or sarilumab **must be** registered with Blueteq (NHSE web-based approval platform) prior to prescribing. The process is described below:

- Go to: https://www.blueteq-secure.co.uk/Trust/default.aspx
- Register for an account if you do not already have one, or log in to an established account.
- Please note registration can be completed using normal UHL email address and should take no longer than a few minutes. You may need to wait for your account to be activated so ideally this step should be completed ahead of need to treat an individual patient.
- Select "Patient" then "Add" from the left hand side of the menu bar.
- Complete the details in the Add High Cost Drugs Patient panel. If the Patient is not currently registered with a GP select "Unregistered NHSE patients as the GP surgery.
- Select "Add request" from the Patient menu bar.
- Make a note of the Blueteq authorisation number – this is required by Pharmacy to release the medication
- The blueteq number should be annotated on the prescription.
- NOTE: There is a separate blueteq form for adults and postpubescent children
- A Blueteq user guide for clinicians is available on Insite

3.7 Dosage and administration

Tocilizumab is now licensed as a treatment for adult patients hospitalised due to COVID-19 who are receiving systemic corticosteroids and require supplementary oxygen or mechanical ventilation and therefore is considered the first line option. Sarilumab should only be used by exception where tocilizumab is unavailable and patients have been made aware that the use of sarilumab in this indication off-label.

Tocilizumab dose:

Tocilizumab will be administered as a single IV infusion at a dose of 8mg/kg estimated or measured body weight, with a maximum total dose of 800mg.
Doses should be banded as per the table below:

Weight	Dose*
<41 kg	8mg/kg, rounded to 20mg
≥41 and ≤ 65 kg	400mg
≥66 and ≤ 90 kg	600mg
>90 kg	800mg

**In the event of shortages, it may be necessary to round doses to the nearest 80mg. You will be advised accordingly by Pharmacy should this be necessary.*

Tocilizumab Administration:

- Calculate the volume of tocilizumab concentrate required for the prescribed dose.
- Remove the equivalent volume from a 100mL sodium chloride 0.9% infusion bag and discard.
- Withdraw the dose from the vial(s) and add to the infusion bag.
- Mix by gently inverting the infusion bag to avoid foaming.
- The prepared tocilizumab musty be administered via an infusion pump
- Infusion speed must be set at 10ml/hr for 15 minutes, and then increased to 130ml/hr for the next 45 minutes.
- After completion of the infusion, at least 20mls of 0.9% saline should be used to flush the drug through the giving set at the same rate as the infusion was given (130ml/hr).

Sarilumab dose:

Sarilumab will be administered as a single fixed dose of 400mg, using two 200mg pre-filled syringes. These syringes are usually licensed for subcutaneous use, and therefore must first be manipulated very carefully to produce an infusion for INTRAVENOUS use.

Sarilumab Administration:

- Allow two x 200mg pre-filled sarilumab syringes to reach room temperature (Typically this is 25-30 minutes)
- Inject the contents of the two syringes into a 100mL sodium chloride 0.9% infusion bag. **Baxter Viaflex® bags should not be used as the short needle on the pre-filled sarilumab syringes may not be long enough to pierce the internal septum of the drug additive port of this bag.**
- Mix by gently inverting the infusion bag ten times to avoid foaming and ensure thorough mixing.
- The prepared sarilumab must be administered using an infusion pump and via a giving set with a 0.2micron (or equivalent) low protein binding in line filter.
- Sarilumab IV infusion can be given peripherally or via central access device.
- Sarilumab should not be infused concomitantly in the same intravenous line with other drugs.
- Infusion speed must be set at 10ml/hr for 15 minutes, and then increased to 130ml/hr for the next 45 minutes.

- After completion of the infusion, at least 20mls of 0.9% saline should be used to flush the drug through the giving set at the same rate as the infusion was given (130ml/hr).

Additional information is available via the injectable medicines guide

Given the uncertainty over evidence of additional benefit as well as the need to maximise available supply a second dose of IL-6 inhibitor should not be considered.

3.8 Monitoring, tracking and follow-up

IL-6 inhibitors are immunosuppresants which can suppress C-Reactive Protein (CRP) response for up to 3 months after administration. 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.
Ensure date of IL-6 inhibitor administration is documented on any discharge summary and the patient is provided with a COVID-19 IL-6 inhibitor discharge information leaflet.

3.9 Supply

Once blueteq has been completed tocilizumab or sarilumab should be ordered via your ward pharmacist. When your ward pharmacist is unavailable it should be ordered via the on-site dispensary pharmacist, or if out of hours via the on-call pharmacist (contacted via switchboard)

4. Education and Training

No new skills required to implement the guideline.

5. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead
Blueteq completed for each prescription	Reviewed by pharmacist	Ongoing – real time	Professionally checking pharmacist

6. Supporting Documents and Key References

Interim Clinical Commissioning Policy: IL-6 inhibitors for Patients Hospitalised with COVID-19 . NHSEI November 2022
Summary of Product Characteristics: RoActemra concentrate for solution for infusion. Roche products Limited November 2022
Summary of Product Characteristics: Kevzara 200 mg solution for injection in pre-filled syringe. Sanofi Genzyme March 2022

7. Key Words

COVID, COVID-19, SARS-COV-2, IL-6,IL-6 inhibitor, Tocilizumab, Sarilumab, Blueteq

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This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	Mohammed Karolia	**Job Title:** Deputy Chief Pharmacist
Reviewed by:	Mohammed Karolia	
Approved by:	**Policy and Guideline Committee**	**Date Approved: 28 June 2023**

REVIEW RECORD			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
February 2023	2	Mohammed Karolia	Previous COVID-19 guideline transferred to PGC template.

DISTRIBUTION RECORD:			
Date	**Name**	**Dept**	**Received**