Tocilizumab for patients hospitalised with COVID-19 (adults)

Tocilizumab (RoActemra®) is a humanised monoclonal antibody against the interleukin-6 (IL-6) receptor. The intravenous infusion preparation has a marketing authorisation in the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. It also has a marketing authorisation for non-COVID-19 clinical indications, which is outwith the scope of this protocol.

The Scottish Medicines Consortium (SMC) collaborated with National Institute for Health and Care Excellence (NICE) on the Multiple Technology Appraisals (MTA) 878, which includes positive treatment recommendations for the following licensed COVID-19 treatments relevant to this guideline; tocilizumab (RoActemra®).

The previous recommendation for the off-label use of sarilumab in COVID-19 has been superseded by NICE MTA 878/ SMC2552, which only recommends the interleukin-6 inhibitor tocilizumab which is licensed for use in COVID-19.

1. Allowed Prescribers

Tocilizumab for the treatment of COVID-19:

- must only be initiated by a Consultant.
- must be prescribed on the Hospital Electronic Prescribing & Medicine Administration (HEPMA) system and on an Infusion Therapy Recording Chart.

2. Eligibility criteria

Hospitalised adult patients are eligible[1] to be considered for **tocilizumab** for the treatment of COVID-19 if they meet all the following eligibility criteria and none of the exclusion criteria:

- aged 18 years or over

AND

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

AND

- Receiving systemic corticosteroids for COVID-19 (see ADTC 358: Corticosteroids in the treatment of suspected or confirmed COVID-19)

AND

- Need supplemental oxygen or mechanical ventilation for COVID-19

The Summary of Product Characteristics (SmPC) for tocilizumab states that the efficacy of tocilizumab has not been established in the treatment of COVID-19 in people who do not have elevated C-reactive protein levels.

[1] *The decision to initiate treatment with tocilizumab should be made by the receiving consultant and with the support from multi-disciplinary colleagues in cases of uncertainty*

3 Exclusions and cautions for use

3.1 Exclusions

Tocilizumab should not be administered in the following circumstances:

- Known hypersensitivity to tocilizumab or to any of the excipients listed in the Summary of Product Characteristics (SmPC)
- COVID-19 patients who are not receiving systemic corticosteroids, as an increase in mortality cannot be excluded in this subgroup.
- Patients with any other concurrent severe active infection.
- Liver enzymes [alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] more than ten times the upper limit of normal
- Absolute neutrophil count of less than 1 x 10^9/L
- Platelet count of less than 50 x 10^9/L

Please refer to the Summary of Product Characteristics (SmPC) for tocilizumab for special warnings and precautions for use specific to when being used for the treatment of COVID-19.

3.2 Cautions

Caution should be exercised when considering treatment with tocilizumab in the following circumstances:

- in patients with a history of recurring or chronic infections or with underlying conditions (e.g. diverticulitis, diabetes, and interstitial lung disease) which may predispose patients to infections
- A pre-existing condition or treatment resulting in ongoing immunosuppression

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.

3.3. Pregnancy, breastfeeding, use in women of childbearing potential and effect on fertility

In **all** cases of pregnancy and breastfeeding, senior Obstetric advice should be sought to ensure that theoretical risks to the fetus (or baby in the case of breastfeeding) do not outweigh proven benefits to the mother. In some cases of breastfeeding, it may be more appropriate to seek advice from a pediatrician.

Clinicians should refer to the SmPCs of tocilizumab for further information on their use in pregnancy, breast feeding, women of childbearing potential and effects on fertility.

In addition the current guidance from the Royal College of Obstetricians and Gynaecologists on Coronavirus (COVID-19), infection in pregnancy should be followed.

The SmPC for tocilizumab currently states "*women of childbearing potential must use effective contraception during and up to 3 months after treatment.*"

4. Dosing schedules, and administration information

- A RoActemra® (tocilizumab) Patient Alert Card should be provided to patients when administered or, if not appropriate at the time, prior to discharge from level 2 or level 3 care.

<table>
<tr><th></th><th>Tocilizumab</th></tr>
<tr><td>Dosing schedule</td><td>Recommended dose of tocilizumab is 8mg/kg to be administered as a single intravenous infusion. The total single dose should not exceed 800mg.
The following dose bandings are suggested for use within defined weight ranges:
<table><tr><th>Weight</th><th>Dose of tocilizumab</th></tr><tr><td><41kg</td><td>8mg/kg, rounded to nearest 20mg</td></tr><tr><td>≥41 and ≤45kg</td><td>360mg</td></tr><tr><td>≥46 and ≤55kg</td><td>400mg</td></tr><tr><td>≥56 and ≤65kg</td><td>480mg</td></tr><tr><td>≥66kg and ≤80kg</td><td>600mg</td></tr><tr><td>≥81 and ≤90kg</td><td>680mg</td></tr><tr><td>≥91kg</td><td>800mg</td></tr></table></td></tr>
<tr><td></td><td>If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of tocilizumab 8 mg/kg may be administered. The interval between the two infusions should be at least 8 hours.</td></tr>
<tr><td>Supplies</td><td>Will be supplied from the pharmacy department
A limited supply for use outwith pharmacy opening hours will also be available from:
• University Hospital Ayr - Emergency Drug cupboard
• University Hospital Crosshouse – Emergency Drug cupboard</td></tr>
<tr><td>Preparation</td><td>Requires to be prepared in clinical areas, refer to the relevant drug monograph within the Medusa Injectable Medicines Guide for details.</td></tr>
<tr><td>Administration</td><td>• Resuscitation and anaphylaxis treatment facilities must be readily available during and for 1 hour after the end of the infusion.
• Should only be administered during daytime hours
• Refer to the relevant drug monograph within the Medusa Injectable Medicines Guide for administration and monitoring instructions.</td></tr>
<tr><td>Monitoring</td><td>Hypersensitivity reactions, including anaphylaxis, have been reported with administration of tocilizumab. If an anaphylactic reaction or other serious hypersensitivity / serious infusion related reaction occurs, immediately discontinue administration and initiate appropriate medications and/or supportive care.
Baseline observations should be recorded using the current NEWS (National Early Warning Score) chart. Baseline observations should be repeated after 15 minutes, then every 30 minutes until 1 hour post infusion. Note that infusion related reactions can occur during or within 24 hours of the infusion and patients should be advised to report any signs.
• Daily monitoring of FBC and LFTs.
• Daily review for evidence of concomitant infection (CRP may decline due to tocilizumab treatment therefore cannot be utilised as indication of concomitant infection therefore clinical review, cultures and consideration of procalcitonin level should be used to guide).</td></tr>
</table>

Combination treatment

IL-6 inhibitors may be administered in combination with baricitinib (as well as corticosteroids, unless contra-indicated), 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.

5. Adverse effects

Refer to the tocilizumab SmPC for further information on adverse effects.

6. Drug Interactions

- No interactions between IL-6 inhibitors with corticosteroids (dexamethasone, hydrocortisone or prednisolone), remdesivir or nMABs (e.g. sotrovimab) or baricitinib are expected.
- Further information on interactions can be found within the tocilizumab SmPC or via University of Liverpool COVID-19 Drug Interactions website.

7. Safety reporting

Any suspected adverse reactions (including congenital malformations and/or neurodevelopmental problems following treatment during pregnancy) from any of the treatments should be reported directly to the MHRA via the dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/.

8. Communication

Treatment with IL-6 inhibitors (e.g. tocilizumab) can lower the ability of the immune system to fight infections. This could increase the risk of getting a new infection or make any infection the patient contracts worse. It also causes prolonged depression of CRP levels, making CRP a less reliable marker of active infection.

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) must explicitly mention that an IL-6 inhibitor (e.g. tocilizumab) has been given and the date of administration.

Clinicians must ensure the GP is aware the patient has received an IL-6 inhibitor by including information on the immediate discharge letter and providing information to the patient to such effect.

10. Bibliography

1. CEM/CMO(2023)001. COVID Therapeutic Alert 2023 1 – Publication of NICE Multiple Technology Appraisal (MTA) – Treatment recommendation for COVID-19, Available from: COVID therapeutic alert 2023 1 – publication of NICE multiple technology appraisal (MTA) – treatment recommendations for COVID-19 (scot.nhs.uk) (accessed 07 April 2023).
2. Scottish Medicines Consortium, SMC 2552 Tocilizumab (RoActemra®) 20mg/mL concentrate for solution for infusion, issued 29 March 2023, updated 06 April 2023. Available from: tocilizumab (RoActemra) (scottishmedicines.org.uk) (accessed 07 April 2023).
3. National Institute for Clinical Excellence (NICE). Multiple Technology Appraisal (MTA) TA878: casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19, published 29 March 2023, updated 05 April 2023. Available from: Overview | Casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19 | Guidance | NICE (accessed 07 April 2023).

4. NICE guideline [NG191]. COVID-19 rapid guideline: managing COVID-19. Published: 23 March 2021. Last updated: 29 March 2023. Available from: Overview | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE (accessed 07 April 2023).
5. RCOG, Royal College of Midwives, Royal College of Paediatrics and Child Health, Public Health England and Public Health Scotland. Coronavirus (COVID-19), infection in pregnancy, Version 16.0: updated Thursday 15 December 2022. Available from: Coronavirus (COVID-19), infection in pregnancy | RCOG (accessed 07 April 2023).
6. RoActemra® (tocilizumab) 20mg/ml concentrate for solution for infusion Summary of Product Characteristics, last updated on eMC 29 November 2022. Available from https://www.medicines.org.uk/emc/product/6673/smpc (accessed 07 April 2023).