17FM.3 TOCILIZUMAB AND SARILUMAB FOR PATIENTS WITH COVID-19 PNEUMONIA (ADULTS)

Colour code:

- Antibiotics highlighted **red** and **bold** are **penicillin** based. They are contraindicated in patients with a history of penicillin allergy with life-threatening reaction e.g. anaphylaxis, angioedema and/or urticaria.
- Antibiotics highlighted *orange* and *italic* belong to either the cephalosporin or carbapenem groups of antibiotic and should be used with caution in patients a history of non-severe penicillin allergy e.g. delayed/minor rash. They are contraindicated if serious penicillin allergy e.g. anaphylaxis or angioedema.
- Antibiotics highlighted green are considered safe to use in patients allergic to penicillin.

This revised guidance is based on the updated NHSE Interim Clinical Commissioning Policies for Tocilizumab[1] and Sarilumab[2]. The choice of agent now depends on a patient meeting all of the eligibility criteria and none of the exclusion criteria for the individual drugs below. Tocilizumab and sarilumab are not licensed for use in COVID-19 and their use is off-label for this indication.

Patient information leaflet: The patient should be provided with the information leaflet - Tocilizumab and Sarilumab Treatment for COVID-19.

Tocilizumab eligibility criteria

- Approval by Consultant in Respiratory Medicine or Intensive Care Medicine. If uncertainty over decision to treat, seek advice from multidisciplinary team (MDT)
- Confirmed COVID-19 test, or the MDT has a high level of confidence that COVID-19 is the most likely diagnosis
- Patient receiving (or have completed a course of) dexamethasone or an equivalent corticosteroid (corticosteroid CAS alert) unless contraindicated

  AND EITHER
  - With a C-reactive protein level of at least 75 mg/L; AND an oxygen saturation of <92% on room air OR requirement for supplemental oxygen; **OR**
  - The patient is within 24 - 48 hours of commencement of respiratory support (high flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation). Patients should be treated as early as possible in their illness.

Tocilizumab exclusion criteria

- Known hypersensitivity to tocilizumab

Tocilizumab cautions

- Co-existing infection that might be worsened by tocilizumab*. Raised procalcitonin levels (>0.5 ng/ml) may indicate a co-existing bacterial infection so the risks/benefits of prescribing of tocilizumab should be carefully considered in this situation.
- Baseline 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)
- Baseline platelet count of <50 x 10^9/L
- Baseline absolute neutrophil count of <2 x 10^9/L
- Pre-existing condition or treatment resulting in ongoing immunosuppression
- Caution is necessary when prescribing tocilizumab where there is a history of diverticulitis

**Any active, severe infection other than COVID-19; 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.*

Sarilumab eligibility criteria (this agent should only be used in critically ill patients)

- Patients should not have already received tocilizumab (or other IL-6 inhibitor)
- Approval by two consultants (one of whom should be experienced in respiratory support)
- Confirmed COVID-19 test or MDT has high level of confidence that COVID-19 most likely diagnosis
- Treated <24 hours with respiratory support (high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation)
- Patients should be treated as early as possible in their critical illness, ideally <24 hours since commencing respiratory support (as defined above). Treatment can be started within 48 hours of starting respiratory support for relevant clinical reasons e.g. transfer of patients.

Sarilumab Exclusion Criteria

- Known hypersensitivity to sarilumab
- Co-existing infection that might be worsened by sarilumab*. Caution with raised procalcitonin levels (>0.5 ng/ml) as this may indicate a co-existing bacterial infection, so risks/benefits of prescribing of sarilumab should be carefully considered
- Baseline 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)
- Baseline platelet count of <150 x 10^9/L
- Baseline absolute neutrophil count of <2 x 10^9/L
- Pre-existing condition or treatment resulting in ongoing immunosuppression

**Any active, severe infection other than COVID-19; 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.*

Pregnancy and women of childbearing potential

Tocilizumab or sarilumab should **not** be used during pregnancy unless clinically necessary. See Summary of Product Characteristics (SPC) for tocilizumab[7] or sarilumab[8] for further information.

Tocilizumab SPC currently states "Women of child bearing potential must use effective contraception during and up to 3 months after treatment." In relation to pregnancy, the SPC 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. For women who are breast-feeding, the SPC states *"It is unknown whether tocilizumab is excreted in human breast milk. The excretion of tocilizumab in milk has not been studied in animals. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with RoActemra should be made taking into account the benefit of breastfeeding to the child and the benefit of RoActemra therapy to the woman."*

Sarilimumab SPC currently states 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. For women who are breastfeeding, the SPC states "*It is unknown whether sarilumab is excreted in human milk or absorbed systemically after ingestion. The excretion of sarilumab in milk has not been studied in animals. Because IgG1 are excreted in human milk, a decision should be made whether to discontinue breastfeeding or to discontinue sarilumab therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman."*

Co-administration

Corticosteroids should be used where appropriate in line with current guidance. There is no interaction of tocilizumab or sarilumab with either dexamethasone or hydrocortisone expected.
There is no interaction of tocilizumab or sarilumab with remdesivir expected.

Blueteq
A Blueteq form (https://www.blueteq-secure.co.uk/Trust/default.aspx) must be completed for each patient.

Minimising the risk of sepsis due to Tocilizumab or Sarilumab

There have been anecdotal reports of severe sepsis in patients with COVID-19 following administration of these agents e.g. Staphylococcal bacteraemia and invasive Aspergillus infections. The risk of infection remains for up to 3 months after administration. As CRP monitoring and the presence of pyrexia cannot be relied on to detect infection, the following is advised following tocilizumab/sarilumab dose:

Whilst an inpatient

- Examine the patient daily for signs of sepsis
- Check procalcitonin levels DAILY for seven days post dose
- As CRP is not a reliable indicator of infection in these patients, procalcitonin may need to be measured at additional points during the patient's stay to assist with sepsis detection.
- If procalcitonin level raised, or clinical condition suggests sepsis: send blood cultures and fungal markers (beta-d-glucan (BDG) and galactomannam (GM)/Aspergillus antigen determination)
- Send any available respiratory samples for culture, including fungal culture

At discharge

- Tocilizumab and sarilumab are immunosuppressants which can suppress CRP response for up to 3 months after administration
- The discharge summary should state that tocilizumab or sarilumab were given and the date administered
- The GP should have a low threshold for giving antibiotics or readmitting if the patient becomes unwell with suspected sepsis during three months following discharge

Empirical antibiotic/antifungal treatment
If there is clinical suspicion of sepsis and/or the procalcitonin is >0.5ng/ml, **piperacillin/tazobactam** treatment should be initiated after relevant samples have been sent. If patient is penicillin-allergic, initiate ciprofloxacin plus vancomycin. If there is poor response to antibacterial treatment after 72 hours, discuss with a Microbiologist regarding starting voriconazole (antifungal agent). Subsequent antibiotic management should follow Trust guidelines, with de-escalation if possible.

Supply
The supply of tocilizumab and sarilumab is available 9 – 5 pm 7 days a week. Outside of these hours, tocilizumab and sarilumab will be supplied as a priority the following morning if highlighted to the ward-based pharmacy team. NOTE: Any delay to administration of tocilizumab and sarilumab due to supply hours does not affect inclusion criteria (i.e. if decision to treat is made within 48 hours of starting organ support but supply falls outside of this 48 hours window due to pharmacy opening hours, treatment should still be given).

Tocilizumab information:

Dosage
Weight-based dosing. To reduce prescribing errors and ease administration, dose banding is recommended:

Weight	Dose
>90 kg	800 mg
>65 and ≤90 kg	600 mg
>40 kg and ≤65 kg	400 mg
≤40 kg	8 mg/kg, rounded to nearest 20 mg

Tocilizumab is given as a single dose. At present, there is no consensus of the criteria for use of a second dose, therefore the use of a second dose is not currently recommended.

Preparation and Administration
The preparation of tocilizumab has been risk-assessed using NPA Patient Safety Alert 20[9] and has an overall risk rating as amber. Based on this risk assessment and review by pharmacy department, tocilizumab in this scenario can be prepared at a ward level. To support this a worksheet has been produced if required (see Appendix 1).

- Dilute required dose in a 100 ml bag of 0.9% sodium chloride, after removing an equivalent volume of saline (total volume 100 ml)
- Infuse over 60 minutes (10 ml per hour for 15 mins, then 130 ml per hour for remaining 45 minutes)
- Can be administered via a central or peripheral line
- Do not infuse concomitantly in the same IV line with other medications
- Flush giving set with 20 ml sodium chloride 0.9% pre and post infusions.
- Monitor pulse, blood pressure, temperature, respiratory rate, and for signs of hypersensitivity reactions[+]. Baseline observations should be measured after 15 minutes, then every 30 minutes until 1 hour post infusion

[+]Hypersensitivity reactions include anaphylaxis, flushing, fever, chills, rash, pruritus, urticaria, headache, hypertension.

Adverse events
Commonly reported adverse events: Upper respiratory tract infections, nasopharyngitis, headache, hypertension and liver transaminase derangement. Refer to SPC for more information on adverse effects. No increased rates of serious adverse events were reported in the trial studies. However, MHRA drug safety update states potential increased risk of serious liver injury.[10]

Sarilumab information:

Dosage
Single dose of 400 mg given via intravenous infusion over 60 minutes.

Preparation and Administration
The preparation of sarilumab has been risk-assessed using NPA Patient Safety Alert 20[5] and has an overall risk rating as amber. Based on this risk assessment and review by pharmacy department, sarilumab in this scenario can be prepared at a ward level. To support this a worksheet has been produced if required (see Appendix 2).

- Two 200 mg pre-filled syringes should be used
- Allow syringes to reach toom temperature (stored in fridge)
- Inject the contents of two syringes into a 100 ml bag of sodium chloride 0.9%
- Invert bag 10 times to mix (do not shake)
- Can be administered via a central or peripheral line
- Do not infuse concomitantly in the same IV line with other medications
- Use infusion immediately. If not possible, infusion may be started within 4 hours of infusion
- Infuse over 60 minutes (10 ml per hour for 15 minutes, then 130 ml per hour for remaining 45 minutes)
- Flush with 20 ml sodium chloride 0.9% at same rate as infusion
- Monitor for infusion related reactions (IRR): Chills, nausea, headache, wheezing, itching, flushing, pyrexia, dizziness. If mild to severe IRR occurs stop treatment and treat symptoms. Reduce infusion rate by at least 50% when re-starting infusion.

Adverse events
Commonly reported adverse events: Neutropenia, liver transaminase derangement, injection site erythema, upper respiratory tract infections, urinary tract infections. Refer to SPC for more information on adverse effects.

Background to guidance

Tocilizumab and sarilumab are recombinant humanised monoclonal antibody that block the interleukin-6 (IL-6) receptor, potentially mitigating the IL-6 mediated systemic and local effects seen within COVID-19. IL-6, which is secreted by monocytes and macrophages, is one of the main drivers of immunologic response and symptoms in patients with cytokine-release syndrome (CRS)[3]. The REMAP-CAP[4] trial has reported with tocilizumab or sarilumab an overall reduction in risk of death of 24% in patients and reduced the time patients spent in the ICU by more than a week on average. The RECOVERY[5] trial have now reported on tocilizumab use in a broad hospitalized population, which indicated that tocilizumab significantly improved survival and other clinical outcomes in patients with hypoxaemia and systemic inflammation. A rapid evidence review[6] published by the National Institute for Health and Care Excellence (NICE) on 20 January 2021 suggested that any mortality or recovery benefit from sarilumab is seen only in the most severely ill patients given sarilumab soon after organ support is started, when any developing organ dysfunction may be more reversible.

Appendix 1: Preparation and Administration of Tocilizumab at Ward Level[11]

1. Wear personal protective equipment (PPE), i.e. gown, gloves, protective eyewear and respirator mask.
2. Prepare in a well-ventilated area in clean utility drug preparation room.
3. Calculate the volume of tocilizumab concentrate required for the prescribed dose and remove the equivalent volume from a 100 ml sodium chloride 0.9% infusion bag using a butterfly needle and discard (see table).

Weight band	Dose	Volume to remove from a 100 ml sodium chloride 0.9% infusion bag	Volume of tocilizumab required	
			400 mg/20 ml vial	200 mg/10 ml vial
≤40 kg	8 mg/kg round to nearest 20 mg	…….	-	……..
>40 kg and ≤65 kg	400 mg	20 ml	20 ml	-
>65 kg and ≤90 kg	600 mg	30 ml	20 ml	10 ml
>90 kg	800 mg	40 ml	40 ml	-

4. Draw up the required volume of tocilizumab SLOWLY to avoid creating foam.
5. Attach the syringe to the butterfly needle and inject SLOWLY and directly into the sodium chloride 0.9% infusion bag to prevent foaming.
6. Mix by gently inverting the infusion bag to avoid foaming. DO NOT SHAKE.
7. Ensure the product solution is clear and free from any precipitation.
8. Infuse over 60 minutes (10 ml per hour for 15 minutes, then 130 ml per hour for remaining 45 minutes)
9. Flush giving set with sodium chloride 0.9% pre and post infusions.
10. Monitor pulse, blood pressure, temperature and respiration rate, and for any signs of hypersensitivity reaction. Baseline observations should be measured after 15 minutes, then every 30 minutes until 1 hour post infusion.

Appendix 2: Preparation and administration of Sarilumab at a ward level[12]

1. Wear personal protective equipment (PPE), i.e. gown, gloves, protective eyewear and respirator mask.
2. Prepare in a well-ventilated area in clean utility drug preparation room.
3. Two 200 mg pre-filled syringes (200 mg/1.14ml) should be used to make a 400 mg dose.
4. Allow syringes to reach toom temperature (stored in fridge).
5. Inject the contents of two syringes into a 100 ml bag of sodium chloride 0.9%.
6. Invert bag 10 times to mix (do not shake).
7. Ensure the product solution is clear and free from any precipitation.
8. Can be administered via a central or peripheral line.
9. Do not infuse concomitantly in the same IV line with other medications.
10. Use infusion immediately. If not possible, infusion may be started within 4 hours of infusion.
11. Infuse over 60 minutes (10 ml per hour for 15 minutes, then 130 ml per hour for remaining 45 minutes).
12. Monitor for infusion related reactions (IRR): Chills, nausea, headache, wheezing, itching, flushing, pyrexia, dizziness. If mild to severe IRR occurs stop treatment and treat symptoms. Reduce infusion rate by at least 50% when re-starting infusion.
13. Flush with 20 ml sodium chloride 0.9% at same rate as infusion.

References

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