Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Interim Guidance for the use of Tocilizumab in the Management of Patients who have Severe COVID-19 with Suspected Hyperinflammation

This document is intended for use by healthcare professionals only.

This guidance is specific to the management of Patients with confirmed Severe COVID-19 with Suspected Hyperinflammation. While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation.

This guidance should be read in conjunction with the National HSE Infection Prevention and Control (IPC) Guidance for Possible or Confirmed COVID-19 .

Summary statement regarding the use of tocilizumab in the management of patients who have severe COVID-19 with suspected hyperinflammation

A formal Evidence Review has been conducted to assess the potential efficacy of tocilizumab in COVID-19. The evidence presented here is current as of 24th March 2020. This is a rapidly evolving area with emerging evidence accruing on a continual basis. Data from real world experience and associated updated evidence will be considered for inclusion in updated versions of this document.

1. Tocilizumab is an experimental medicine in the context of the management of severe COVID-19 disease. It must only be considered in patients with a care plan that includes a full range of critical care support and severe COVID-19 with suspected hyperinflammation. It must only be prescribed following multidisciplinary input and a consultant decision (see Treatment Criteria).

2. The use of investigational or off-label medicinal products to treat patients with confirmed COVID-19 is at an experimental stage. The evidence of clinical efficacy is lacking. Patients (or their next of kin, by phone) should be adequately informed about the uncertain efficacy, and respective toxicities of the agents, and their consent obtained. Treatment should be initiated in the context of an ethically approved clinical trial wherever possible.

3. Cytokine release syndrome (CRS), also termed hyperinflammation[1], is a complication of COVID-19 and is associated with high morbidity.

4. Early identification of hyperinflammation in COVID-19 patients is essential. Serial monitoring of ferritin, C-Reactive Protein, fibrinogen, D-dimers and other inflammatory markers may identify hyperinflammation and allow early intervention. Significant elevations of C-Reactive Protein, D-Dimers and Ferritin correlate with increased levels of IL-6 and poor outcome in patients with severe COVID-19 infection.

5. The evidence continues to emerge for the use of tocilizumab in this setting and therefore every effort should be made to collect relevant clinical outcomes. Each hospital should have a designated a member of staff to co-ordinate tocilizumab prescription and registry data.

[1] Note: The terms CRS and hyperinflammation are used interchangeably in this document.

Patient selection (with input from specialist multidisciplinary team)[2,3]

Clinical judgment will be required for all cases; treatment with tocilizumab must only be inititated following specialist consultation with local critical care medicine, haematology, infection specialists and consultant of record.

Guidance for use of IL6 inhibitor tocilizumab in severe-COVID19 with suspected hyperinflammation (RoActemra® 20mg/ml)

Treatment Criteria	1. Treatment must only be initiated after consultant-level discussion in a multidisciplinary setting that includes critical care medicine, haematology, infection specialists and consultant of record. Treatment should be initiated in the context of an ethically approved clinical trial wherever possible. **AND** 2. Hospitalised with confirmed COVID-19 pneumonia evidenced with X-ray or CT scan **AND** ≥1 of the following: - Blood oxygen saturation ≤93% **AND/OR** - PaO_2/FiO_2 ratio <300mmHg (SaO_2/FiO_2 ratio may be used if PaO_2/FiO_2 unavailable; an SaO_2/FiO_2 ratio <330mmHg is equivalent to a PaO_2/FiO_2 ratio <300mmHg) **AND** 3. Established presence of hyperinflammation: assessment and serial monitoring of ferritin, C-Reactive Protein, fibrinogen, D-dimers and other inflammatory markers. Significant elevations of C-Reactive Protein, D-Dimers and Ferritin correlate with increased levels of IL-6 and poor outcome in patients with severe COVID-19 infection. **AND** 4. Exclusion of acute severe infection from sources other than SARS-CoV2.

[2] These criteria are drawn from The SIMIT, Handbook for the care of people with COVID-19 disease (Italy) http://www.simit.org/medias/1568-covid19-vademecum-20-13-marzo-2020.pdf and

[3] The University of Michigan Inpatient Guidance for diagnosis & treatment of COVOD-19 in adults & children http://www.med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf

[5] National Health Committee of the People's Republic of China. China's National Health Commission treatment guidelines 7th version [Internet]. Beijing; 2020 [cited 2020 Mar 16]. Available from: http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml

Recommended dose	Data continues to emerge on dosing in COVID-19; the following recommendations are adopted from China's National Health Commission treatment guidelines[5] and The University of Michigan Inpatient Guidance for diagnosis & treatment of COVID-19 in adults & children[4]: Recommended dosing in adults (Specialist Paediatric advice required for patients aged under 18 years old): - 8mg/kg (maximum 800mg per dose) as a single intravenous infusion. Dose rounding to the nearest whole vial is recommended. Vial sizes available may include 80mg, 200mg, and 400mg. - One additional dose may be considered 8-12 hours later if clinical symptoms worsen or there is no improvement; a maximum of 2 doses per course in severe COVID-19 is recommended; subject to drug access. For infusion details see *Route and method of administration* section below. *Note: The dose indicated for the management of Chimeric Antigen Receptor T-cell (CAR-T) related CRS is higher than has been used in practice for the treatment of hyperinflammation in severe COVID19. The dose in CAR-T related CRS is 8mg/kg (12 mg/kg in patients <30 kg). Dose may be repeated every 8 hours for up to three doses in a 24-hour period. Maximum of 4 doses total over the entire course of CRS.*
Contraindications	Hypersensitivity to the active substance or to any of the excipients. Acute, severe infections. NB Decisions in critically ill patients must involve multidisciplinary input; treatment must only be initiated following Consultant-level multidisciplinary specialist input (see *Treatment Criteria* section). Where patients have additional co-morbidities which may negatively impact on the outcome careful consideration should be given to whether tocilizumab should be used.
Serial Monitoring	Serial monitoring of the following parameters is recommended: ▪ Full Blood Count ▪ *Ferritin ▪ *C-Reactive Protein ▪ *Fibrinogen ▪ *D-dimers * *Increasing levels may be indicative of hyperinflammation* Assessment and serial monitoring of pro-inflammatory markers, including IL-6 (if available), may support the diagnosis of hyperinflammation. Procalcitonin if available, to help outrule bacterial superinfection. Patients with severe or life-threatening CRS frequently have cytopenias or elevated ALT or AST due to the CRS.
Side effects	Most common adverse reactions (incidence of at least 5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, injection site reactions. Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with tocilizumab treatment. See Summary of Product Characteristics (SmPC) for full list of side effects; available from: https://www.medicines.ie/medicines/roactemra-20-mg-ml-concentrate-for-solution-for-infusion--33648/smpc
Renal impairment GFR (mL/min)	Dose as in normal renal function. In patients undergoing renal replacement therapies (APD/CAPD/HD/HDF/High flux/CAV/VVHD) – unknown dialysability. Dose as in normal renal function. Use with caution.
Hepatic impairment	The safety and efficacy of tocilizumab has not been studied in patients with hepatic impairment. The marketing authorisation holder cannot advise on any dose

	adjustments.
Warnings	Risk of serious infection: Increased risk of serious infection including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving tocilizumab.
Drug	Tocilizumab (RoActemra ®) 20 mg/mL concentrate for solution for infusion. Store vials in a refrigerator (2°C–8°C)
Licence	Unlicensed for the management of patients who have severe COVID-19 with suspected hyperinflammation. Tocilizumab is licensed for the management of cytokine release syndrome following treatment with CAR-T and also in the management of rheumatoid arthritis.
Route and method of administration	<u>Patients ≥30kg</u> Withdraw a volume of sterile, non-pyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection from a 100 mL infusion bag, equal to the volume of Tocilizumab concentrate required for the patient's dose, under aseptic conditions. The required amount of Tocilizumab concentrate (0.4 mL/kg) should be withdrawn from the vial and placed in the 100 mL infusion bag. This should be a final volume of 100 mL. To mix the solution, gently invert the infusion bag to avoid foaming. Administer by intravenous (I.V.) infusion over 60 minutes.