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 .

Key changes to version 5 of Interim Guidance for the use of Tocilizumab in the Management of Patients who have Severe COVID-19 with Suspected Hyperinflammation are highlighted throughout the text.

<table>
<tr><td colspan="2">Protocol: Interim Guidance for the use of Tocilizumab in the Management of Patients who have Severe COVID-19 with Suspected Hyperinflammation</td><td>Version 1 Published: 20 Mar 2020
Updated Version 5 Published: 02 Sep 2020
Review Date: 31 Oct 2020</td><td>Version number: 5</td></tr>
<tr><td>Protocol Code: COVID19-TOCILIZUMAB</td><td>Approved by: Dr Vida Hamilton, HSE National Clinical Advisor and Group Lead, Acute Hospitals</td><td>Contributors: Prof C Bergin, Prof P Browne, Prof P Murray, Prof M O'Dwyer, Dr N Conlon, Prof D Kane, Prof J Laffey, Prof A Nichol, C Ní Choitir, Dr R Adams, Dr A O'Leary, F King, P Gilvarry.</td><td>Page 1 of 8</td></tr>
<tr><td colspan="4">Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibly of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer
This information is valid only on the day of printing, for any updates please check: https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/</td></tr>
</table>

The following HSE interim guidance and advisory statements should also be considered for the management of patients with COVID-19, as appropriate (available from: https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/):

- *HSE Interim Guidance for the Use of Antiviral Therapy in the Clinical Management of Acute Respiratory Infection with SARS-CoV-2 (COVID-19)*
- *HSE Interim Position Statement on the Use of Human Normal Intravenous Immunoglobulin (IVIg) in the Management of COVID-19.*
- *HSE Interim Position Statement on the use of Dexamethasone in the Management of COVID-19.*

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

This guidance is informed by the COVID-19 Evidence Review Group (ERG) Rapid Evidence Review "Tocilizumab in the management of patients who have severe COVID-19 infection with suspected hyperinflammation" (version 4) published on 21 Aug 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. If treatment is being considered, 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. Consent should be obtained as detailed in the *HSE National Consent Policy* (available online at: https://www.hse.ie/eng/about/who/qid/other-quality-improvement-programmes/consent/national-consent-policy-hse-v1-3-june-2019.pdf). Treatment should be initiated in the context of an ethically approved clinical trial wherever possible. Information on on-going clinical trials, including those recruiting, is available on the EU CT Register for COVID trials (https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19) or www.clinicaltrials.gov. Information on the regulatory and ethical approvals obtained for clinical trials is available from the Office for National Research Ethics Committees (nationaloffice@nrec.ie).

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

4. High-quality evidence to support clinical decision making, including the timing of administration and the identification of a population likely to achieve benefit from tocilizumab in the management of COVID-19, is not yet available. The evidence published to date are predominantly small, single centre, non-randomised studies with sub-optimal methodological quality. The therapeutic benefit reported in observational studies has not yet been replicated in randomised controlled trials (RCTs). Preliminary reports emerging from unpublished RCTs, to date, have not demonstrated therapeutic benefit versus standard of care. Data from the RECOVERY trial and the full publication of the COVACTA trial are awaited. As the evidence continues to emerge for the use of tocilizumab in this setting every effort should be made to collect relevant clinical outcomes (e.g. WHO Core Outcomes and suggested safety outcome measures, Appendix 1). 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; if treatment with tocilizumab is being considered it must only be initiated 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. If treatment is being considered, it 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[3]: 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. - In exceptional circumstances, one additional dose may be considered 8-12 hours later if clinical symptoms worsen or there is no improvement. The decision to administer a second dose must only be made following Consultant-level multidisciplinary specialist input (see *Treatment Criteria* section). 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. Healthcare Professionals are asked to report any suspected adverse reactions via Health Products Regulatory Authority (HPRA) Pharmacovigilance: www.hpra.ie .
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	Patients ≥30kg 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.

Appendix 1 – Suggested Outcome Measures for Patients Treated Outside of a Clinical Trial

Reports continue to emerge suggesting tocilizumab may have a role in the management of severe COVID-19 with suspected hyperinflammation. In the absence of the drug being administered in a formal clinical trial, the following proposed outcomes should be considered:

WHO Core Outcome Measure Set for Clinical Studies of COVID-19 Infection *(unpublished recommendations from the WHO Working Group on the Clinical Characterization of COVID-19 infection,* http://www.comet-initiative.org/Studies/Details/1538*)*:

Domain	Measure
Viral burden	COVID-19 semiquantitative viral RNA measured by qPCR cycle threshold (Ct) in nasopharyngeal or throat swab, sputun, or upper of lower repiratory secretions
Survival	All-cause mortality at hospital discharge or 60 days
Clinical progression	WHO Clinical Progression Scale, measured daily over course of study

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
	Symptomatic; Independent	2
	Symptomatic; Assistance needed	3
Hospitalized: Mild disease	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: Severe disease	Hospitalized; Oxygen by NIV or High flow	6
	Intubation & Mechanical ventilation, pO_2/FIO_2 ≥150 or SpO_2/FIO_2≥200	7
	Mechanical ventilation pO_2/FIO_2<150 (SpO_2/FIO_2 <200) **or** vasopressors	8
	Mechanical ventilation pO_2/FIO_2<150 **and** vasopressors, dialysis, or ECMO	9
Death	Dead	10

Notes.

1. If hospitalized for isolation only, record status as for ambulatory patient
2. If pO_2 not available, use SpO_2/FIO_2 ratio with a cutoff of 200 [18]

Suggested Safety Outcome Measures:

Any Serious Adverse Event believed with a reasonable probability to be due to tocilizumab treatment, including, but not limited to:

- Secondary opportunistic infection, out of keeping with clinical disease
- Severe thrombocytopenia, out of keeping with clinical disease
- Severe neutropenia, out of keeping with clinical disease

- Increase in LFTs to 5x upper limit of normal
- Gastrointestinal perforation
- Allergic reactions, including anaphylactic reactions and angioedema