



Department
of Health &
Social Care



The Scottish
Government
Riaghaltas na h-Alba



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Department of
Health

An Roinn Sláinte
Máinystrie O Poustie



Interim Position Statement

Interim Position Statement: Tocilizumab for patients admitted to ICU with COVID-19 pneumonia (adults)

25 November 2020

Introduction

In response to the public health emergency posed by coronavirus disease 2019 (COVID-19), NHS England, working with the Devolved Administrations (DAs), has established a rapid policy/position development process to aid clinicians in offering best care and advice to patients with or at risk of COVID-19 across the UK. This document sets out the interim clinical position for the use of tocilizumab in patients with COVID-19.

Tocilizumab has marketing authorisations for rheumatoid arthritis, juvenile idiopathic arthritis, temporal arteritis and for cytokine release syndrome as part of CAR-T therapy, and NHS England commissions off-label use of tocilizumab for Takayasu arteritis and Still's Disease. The use of tocilizumab in COVID-19 is also off label.

Interim position

Until the full data from the [REMAP-CAP](#) and [RECOVERY](#) trials are available, the off-label use of tocilizumab within critical care should follow the criteria and information described in this interim clinical position. The trial Data and Safety Monitoring Board (DSMB) has determined that it is ethically imperative to withdraw the standard-of-care control arm of the immune modulator domain of the REMAP-CAP trial. The domain, though, will continue as there are other medicines that need evaluation that may be more effective than tocilizumab. Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board/hospital/trust's drugs and therapeutics committee (or equivalent).

Evidence summary

Emergent (non-published) data from the immune modulation arm of the REMAP-CAP trial indicate positive benefits with the use of tocilizumab in patients admitted to an intensive care unit (ICU). This interim position statement provides further information to clinicians

considering prescribing tocilizumab when the internal governance arrangements (described above) are in place. Until the results of the REMAP-CAP trial are published, the eligibility and exclusion criteria for this interim position statement have been drawn from those used in this trial and the Summary of Product Characteristics (SmPC) for [tocilizumab](#). Clinicians are encouraged to check the SmPC carefully.

Implementation

Eligibility criteria

Patients must meet all of the eligibility criteria and none of the exclusion criteria. Patients are eligible for tocilizumab if:

- Admitted to ICU with severe pneumonia requiring respiratory support¹, such as high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation; and
- COVID-19 infection is confirmed by microbiological testing or where a multidisciplinary team has a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis

Exclusion criteria (drawn from REMAP-CAP and/or SmPC)

Tocilizumab should not be administered in the following circumstances:

- Known hypersensitivity to tocilizumab [REMAP-CAP and SmPC contraindication]
- Co-existing infection² that might be worsened by tocilizumab [SmPC contraindication]
- More than 24 hours has elapsed since ICU admission or more than 24 hours after starting respiratory support (whichever is the greater) [REMAP-CAP]
- A 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) [REMAP-CAP and SmPC special warning and precautions for use]
- A baseline platelet count of less than $50 \times 10^9/L$ [REMAP-CAP and SmPC special warning and precautions for use]
- A baseline absolute neutrophil count of less than $2 \times 10^9/L$ [SmPC special warning and precautions for use]
- A pre-existing condition or treatment resulting in ongoing immunosuppression [SmPC special warning and precautions for use]

Pregnancy and women of childbearing potential

The REMAP-CAP trial excluded pregnant women, whereas the RECOVERY trial has included pregnant women. Please check the SmPC for tocilizumab, which currently states: “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. Tocilizumab should not be used during pregnancy unless clearly necessary.”

¹ Or admitted to ICU with organ failure requiring support as infusion of vasopressor or inotropes or both.

² Any active, severe infection other than COVID-19; caution is advised when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections.

Dose

The recommended dose is 8mg/kg to be administered as an intravenous infusion. The total dose should not exceed 800mg. Tocilizumab should be diluted in a 100mL bag of 0.9% sodium chloride, after removing an equivalent volume of saline (total volume 100mL) and given over 1 hour³. A single dose is to be administered, with the option to repeat a dose in 12-24 hours after the initial dose if there has not been sufficient clinical improvement.

Tocilizumab should not be infused concomitantly in the same IV line with other medications.

Co-administration

Corticosteroids

Administration of systemic dexamethasone or hydrocortisone is recommended in the management of patients with severe or critical COVID-19. Corticosteroids are not suggested in non-severe COVID-19 disease. Updated WHO guidance on the use of systemic corticosteroids in the management of COVID-19 can be found [here](#).

There is no interaction of tocilizumab with either dexamethasone or hydrocortisone expected. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (<https://www.covid19-druginteractions.org/checker>).

Remdesivir

The Clinical Commissioning Policy for the use of remdesivir in hospitalised patients with COVID-19 who require supplemental oxygen can be found [here](#). There is no interaction of tocilizumab with remdesivir expected.

Safety reporting

Any suspected adverse drug reactions (ADRs) for patients receiving tocilizumab should be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: <https://coronavirus-yellowcard.mhra.gov.uk/>

Plain language summary

COVID-19 is a disease caused by a coronavirus (named SARS-CoV-2) causing many different symptoms, the most common being fever, loss of sense of taste and smell and cough. Tocilizumab is an antibody that targets a protein called interleukin-6 (IL-6), which is thought to be important in the COVID-19 pathway. This position outlines the criteria for the use of tocilizumab to treat people with COVID-19 in intensive care in hospital and in line with current evidence.

Overview

The condition

COVID-19 manifests predominantly as a respiratory illness, of widely varying clinical severity. At the most severe end of the spectrum COVID-19 results in severe pneumonia and respiratory failure with the need for mechanical ventilation. Hyperinflammatory states caused by a cytokine release syndrome that lead to organ dysfunction beyond the respiratory tract have also been well described.

³ The study protocol recommended: 10ml/hr for first 10mins then 130ml/hr for the remaining 45mins followed by a 20ml n/s flush.

Intervention

Tocilizumab is a recombinant humanised monoclonal antibody that inhibits both membrane-bound and soluble interleukin-6 (IL-6) receptors. IL-6 is a pro-inflammatory cytokine that is a key driver behind the cytokine-release syndrome seen in patients with severe COVID-19. By targeting IL-6 receptors, tocilizumab may mitigate the cytokine-release syndrome and prevent progression of disease. Tocilizumab for intravenous use has a marketing authorisation for adults in the treatment of rheumatoid arthritis. Tocilizumab for intravenous use has marketing authorisations for children 2 years and over in the treatment of active systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis and cytokine release syndrome (CRS). Tocilizumab use in COVID-19 is off-label. Reported adverse effects include upper respiratory tract infections, nasopharyngitis, headache, hypertension and liver transaminase derangement (<https://www.medicines.org.uk/emc/product/6673/smpc>).

Equality statement

Promoting equality and addressing health inequalities are at the heart of the four nations' values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Governance

Off-label use of medication

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board/hospital/trust's drugs and therapeutics committee (or equivalent).

Data collection requirement

Provider organisations in England should register all patients using prior approval software (alternative arrangements in Scotland, Wales and Northern Ireland will be communicated) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Clinical outcome reporting

Hospitals managing COVID-19 patients are strongly encouraged to submit data through the ISARIC 4C Clinical Characterisation Protocol (CCP) case report forms (CRFs), as coordinated by the COVID-19 Clinical Information Network (CO-CIN) (<https://isaric4c.net/protocols/>).

Effective from

This interim position statement will be in effect from the date of publication.

Position review date

This is an interim position statement, which means that the full process of policy production has been abridged. This position will need review as new trial data emerges.