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1. Directors of Pharmacy
2. Medical Directors NHS Boards

25 November 2020

Dear Healthcare Professional,

COVID-19 THERAPEUTIC ALERT – INTERIM POSITION STATEMENT ABOUT THE USE OF TOCILIZUMAB FOR ADULT PATIENTS ADMITTED TO ICU WITH COVID-19 PNEUMONIA

Please see the attached letter about the off label use of tocilizumab for adult patients admitted to ICU with COVID-19 pneumonia. I would be grateful if you could cascade this information to relevant colleagues.

Could all Directors of Pharmacy please forward this alert to:-

- Hospital Pharmacists

Please could Medical Directors forward this alert to:-

- Accident & Emergency Departments
- Directors of Public Health
- Consultants in Communicable Diseases
- Relevant Clinics
- Chief Executives of NHS Board

Thank you for your co-operation.

Yours sincerely

IRENE FAZAKERLEY
Pharmacy and Medicines Division

Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

CEM/CMO/2020/038 25 November 2020

Publication of an interim position statement: Tocilizumab for patients admitted to ICU with COVID-19 pneumonia (adults)

Summary

Following early positive signals of benefit from the immune modulation therapy domain of the REMAP-CAP platform trial, a UK wide position statement has been agreed to support off-label prescribing and access to tocilizumab, administered intravenously, for eligible COVID positive patients in the intensive care setting.

The interim position statement will be reviewed as further evidence becomes available, including from the REMAP-CAP trial.

Action

NHS acute trusts / health boards are asked to take the following immediate steps to support treatment of patients admitted to intensive care with COVID-19:

1. REMAP-CAP trial centres should continue to enrol patients into the study. 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 immunomodulatory domain. However, the domain will continue, with all patients receiving an immune modulator to determine relative effectiveness.

2. **Confirm whether or not the organisation wishes to prescribe tocilizumab in the treatment of patients admitted to intensive care with COVID-19 outside of a trial.** Any provider organisation treating patients with this intervention, as an off-label product, will be required to assure itself that the necessary internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board / trust's drugs and therapeutics committee (or equivalent).

3. In England, trusts should register to participate in COVID-19 specific tocilizumab supply arrangements via Blueteq™. Blueteq should also then be used to confirm pre-authorisation for individual patients. HSC Trusts in Northern Ireland should liaise with the Regional Pharmaceutical Procurement Service to register interest. In Scotland, Health Board Directors of Pharmacy should notify NHS National Procurement if they wish to participate. Health Boards in Wales should notify the All Wales Specialist Procurement Pharmacist of their intention to participate

4. Ensure that the criteria described in the interim position statement are used to identify patients with COVID-related pneumonia who may be potentially suitable for treatment with tocilizumab. In the absence of a confirmed virological diagnosis, tocilizumab

should only be used when a multidisciplinary team has a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis.

5. Continue to order tocilizumab supply through existing (business as usual) routes. Arrangements are being made with Roche to secure sufficient supply to the UK to meet potential COVID-19 treatment requirements, alongside existing (licenced) clinical indications. The additional supply will be managed by providing an indicative maximum order 'cap' by hospital / trust (based on modelled intensive care activity), for those organisations who have formally confirmed they wish to participate. Retrospective reimbursement of medicines costs will continue to be managed as usual through the excluded drugs funding route in England. Further advice will follow for Northern Ireland, Scotland and Wales.

6. Maintain access to intravenous tocilizumab for existing (non COVID-19) indications including rheumatoid arthritis (where appropriate), paediatric indications and treatment of cytokine storm (CRS) following CAR-T therapy. With the exception of CRS, patients can alternatively be switched to the subcutaneous formulation of tocilizumab. To assess suitability for available subcutaneous formulations for rheumatoid arthritis (RA) and paediatric arthritis patients, please consult the relevant Summary of Product Characteristics.

7. Provide regular updates on the stock position to trust / hospital and regional procurement pharmacy lead / chief pharmacists.

Product Details

Tocilizumab (RoActemra®) is supplied to the UK by Roche Chugai. It is a humanised monoclonal antibody against the interleukin-6 (IL-6) receptor.

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 CAR-induced cytokine release syndrome (CRS).

The published interim position statement covers off-label use of tocilizumab in adults as an intravenous infusion.

Prescribing

Tocilizumab is not licensed for use in COVID-19. As such clinicians prescribing tocilizumab for this indication should follow trust / hospital governance procedures in relation to the prescribing of unlicensed/off label medicines. Further information on the prescribing of unlicensed/off label medicines can be found here:

https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines#paragraph-71

Administration

Tocilizumab should be administered as an intravenous infusion at a dose of 8mg per kg, up to a maximum dose of 800mg.
A second infusion may be given after 12-24 hours if after the initial dose 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.

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.

For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Distribution

- NHS Trusts (NHS boards in Scotland and Wales)
- Regional Medical Directors
- Regional Chief Pharmacists
- Lead/Senior Pharmacists and Regional Procurement Pharmacy Leads
- Trust/Hospital Medical Directors to circulate to medical and nursing staff managing COVID-19 patients

Enquiries

England: enquiries from NHS trusts in England should in the first instance be directed to your trust pharmacy team who will escalate issues to the Regional Chief Pharmacist and national teams if required. Further information can be requested from the dedicated email address: england.spoc-c19therapeutics@nhs.net.

Northern Ireland: enquiries from hospitals in Northern Ireland should in the first instance be directed to your hospital pharmacy team who will escalate issues to the Regional Pharmaceutical Procurement Service or Pharmaceutical Directorate at the Department of Health if required Further information can be obtained by contacting RPHPS.Admin@northerntrust.hscni.net

Scotland: enquiries from hospitals in Scotland should in the first instance be directed to your hospital pharmacy team who will escalate issues to either NHS National Procurement or the Scottish Government's Medicines Policy Team if required. Contact should be made using the following emails: nss.nhssmedicineshortages@nhs.scot or medicines.policy@gov.scot

Wales: enquiries from hospitals in Wales should in the first instance be directed to the health board's Chief Pharmacist who will escalate issues to the Pharmacy and Prescribing Team at Welsh Government if required. Enquiries to the Welsh Government should be directed to: COVID-19.Pharmacy.Prescribing@gov.wales

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 support[1], 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 infection[2] 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 x 10^9/L [REMAP-CAP and SmPC special warning and precautions for use]
- A baseline absolute neutrophil count of less than 2 x 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 hour[3]. 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.