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1. Directors of Pharmacy
2. Medical Directors NHS Boards

8 January 2021

Dear Healthcare Professional,

COVID-19 THERAPEUTIC ALERT – INTERLEUKIN-6 INHIBITORS (TOCILIZUMAB OR SARILUMAB) FOR PATIENTS ADMITTED TO ICU WITH COVID-19 PNUEMONIA (ADULTS)

Please see the attached letter about the findings of the REMAP-CAP trial about the recovery benefits for tocilizumab or sarilumab, over and above standard care for ICU patients 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
- Community 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

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Pharmacy and Medicines Division

Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

CEM/CMO/2021/001 8 January 2021

Interleukin-6 inhibitors (tocilizumab or sarilumab) for patients admitted to ICU with COVID-19 pneumonia (adults)

Summary

The REMAP-CAP trial has reported a finding of survival and time to recovery benefits for tocilizumab or sarilumab, over and above current standard of care (including corticosteroids), in the immune modulation therapy domain of the REMAP-CAP platform trial. Mortality was reported as 35.8% in the placebo group, compared to 27% in the treatment group, an overall reduction in the risk of death of 24%. The treatment also reduced the time patients spent in the intensive care unit (ICU) by more than a week on average. The published UK wide Interim Position Statement has therefore been revised to support access to either tocilizumab or sarilumab (when available), administered intravenously, for eligible COVID-19 positive patients in the intensive care setting.

As supply of sarilumab is more limited at the current time, provision is likely to need to initially focus predominantly on tocilizumab. Initial stocks of additional tocilizumab supply for the UK have been secured.

Work is now underway to develop a UK clinical commissioning policy for tocilizumab and sarilumab, which will be based on a NICE review of the available research evidence. The policy will replace the Interim Position Statement.

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. RECOVERY trial sites should continue to enrol patients into the study to help determine whether tocilizumab has a role in the future routine treatment of the wider cohort of admitted COVID-19 positive patients.

2. **Organisations are encouraged to consider prescribing either tocilizumab or sarilumab in the treatment of patients admitted to intensive care with COVID-19 pneumonia.** Any organisation treating patients with either intervention, as off-label products, 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 drugs and therapeutics committee, or equivalent.

3. In England, trusts should register (by site) to participate in COVID-19 specific tocilizumab and sarilumab supply arrangements, respectively, 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 revised Interim Position Statement are used to identify patients with COVID-19 related pneumonia who may be potentially suitable for treatment with tocilizumab or sarilumab. In the absence of a confirmed virological diagnosis, tocilizumab or sarilumab 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 have been made with Roche CHUGAI to secure initial supply to the UK to meet potential COVID-19 treatment requirements, alongside existing (licensed) clinical indications. For those organisations who have formally confirmed they wish to participate, the additional supply will be managed by providing an indicative maximum order 'cap' by hospital / trust (based on modelled intensive care activity). Retrospective reimbursement of medicines costs will continue to be managed as usual through the excluded drugs funding route in England. Further advice on this 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.

7. Maintain access to subcutaneous sarilumab for existing rheumatoid arthritis patients. Updates will be provided on additional sarilumab supply, via pharmacy lead networks and their equivalents in Northern Ireland, Scotland and Wales, as soon as further information is available.

8. Provide regular updates on the stock position to trust / hospital and regional pharmacy procurement 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).

Sarilumab (Kevzara®) is supplied to the UK by Sanofi (Aventis Pharma Ltd). It is a human monoclonal antibody that specifically binds to interleukin-6 receptors and blocks the activity of pro-inflammatory cytokines.

Sarilumab for subcutaneous use has a marketing authorisation for adults with moderate to severe rheumatoid arthritis.

The published Interim Position Statement covers off-label use of both tocilizumab and sarilumab in adults as an intravenous infusion.

Prescribing

Tocilizumab and sarilumab are not licensed for use in COVID-19. As such, clinicians prescribing either tocilizumab or sarilumab for this indication should follow trust / hospital governance procedures in relation to the prescribing of off-label medicines.

Further guidance on the prescribing of off-label medicines can be found below:

- https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities
- 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.
The following dose bandings are suggested:

Weight	Dose
<41kg	8mg/kg, rounded to 20mg
≥ 41kg and ≤ 45kg	360mg
≥ 46kg and ≤ 55kg	400mg
≥ 56kg and ≤ 65kg	480mg
≥ 66kg and ≤ 80kg	600mg
≥ 81kg and ≤ 90kg	680mg
≥91kg	800mg

A second infusion may be given after 12-24 hours if after the initial dose there has not been sufficient clinical improvement.

Sarilumab should be administered as a single dose of 400mg as an intravenous infusion.

Neither Tocilizumab nor sarilumab should 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 or sarilumab 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 either tocilizumab, or sarilumab, 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: Interleukin-6 inhibitors (tocilizumab or sarilumab) for patients admitted to ICU with COVID-19 pneumonia (adults)

8 January 2021

Interim position

Clinicians should consider prescribing intravenous tocilizumab following the criteria defined below for patients in intensive care. Intravenous sarilumab could be considered as an alternative (if available).

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

Emergent (as yet not peer-reviewed) data from the immune modulation arm of the REMAP-CAP trial indicate sizeable positive benefits with the use of tocilizumab or sarilumab in patients admitted to an intensive care unit (ICU). In the REMAP-CAP trial, mortality was reported as 35.8% in the placebo group, compared to 27% in the treatment group, an overall reduction in the risk of death of 24%. The treatment also reduced the time patients spent in ICU by more than a week on average. Most patients (over 80%) under evaluation in the REMAP-CAP trial were also treated with a corticosteroid (Corticosteroid CAS Alert), so the effect is thought to be supplementary to those from corticosteroids. This Interim Position Statement provides further information to clinicians considering prescribing tocilizumab or sarilumab when the internal governance arrangements (described above) are in place. The eligibility and exclusion criteria for this Interim Position Statement have been drawn from those used in the REMAP-CAP trial and the Summary of Product Characteristics (SmPC) for tocilizumab and sarilumab. Clinicians are encouraged to check the appropriate SmPC carefully.

Implementation

Eligibility criteria

Patients must meet all of the eligibility criteria and none of the exclusion criteria. Patients are eligible to be considered for tocilizumab or sarilumab 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 intervention SmPC)

Tocilizumab or sarilumab should not be administered in the following circumstances:

- Known hypersensitivity to tocilizumab or sarilumab [REMAP-CAP and SmPC contraindication]
- Co-existing infection[2] that might be worsened by tocilizumab or sarilumab [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]

<u>Pregnancy and women of childbearing potential</u>

The REMAP-CAP trial excluded pregnant women, whereas the RECOVERY trial has included pregnant women. Please check the relevant SmPC for either tocilizumab or sarilumab. The SmPC for sarilumab and tocilizumab currently states: “Women of childbearing potential must use effective contraception during and up to 3 months after treatment.” In relation to use in pregnancy, the SmPC for tocilizumab states there is no adequate data for the use in pregnant women. In relation to use in pregnancy, the SmPC for sarilumab states there is limited 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. Tocilizumab or sarilumab should not be used during pregnancy unless clinically 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 or sarilumab in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections.

Dose

Tocilizumab

The recommended dose of tocilizumab 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.**

Sarilumab

The recommended dose of sarilumab is 400mg to be delivered as a once-only intravenous infusion. Sarilumab is available as a pre-filled syringe. Two 200mg doses should be used to make up the total 400mg dose. 400mg of sarilumab 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]. **Sarilumab 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. Tocilizumab and sarilumab should not be regarded as alternatives to corticosteroids.

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

Safety reporting

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

Marketing authorisation

Tocilizumab delivered intravenously has marketing authorisation for use in moderate to severe active rheumatoid arthritis, some forms of juvenile idiopathic arthritis and for cytokine release syndrome as part of CAR-T therapy. NHS England also commissions off-label use of tocilizumab for Takayasu arteritis and Still's Disease. Sarilumab has marketing authorisation

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

for subcutaneous use in adults with moderate to severe active rheumatoid arthritis. The use of both tocilizumab and sarilumab in COVID-19 is off label.

Governance

Off-label use of medication

Any provider organisation treating patients with these interventions 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 updated 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. Development of a clinical commissioning policy will replace this Interim Position Statement.