Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

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

Summary

The published UK Interim Clinical Commissioning Policy for tocilizumab has been updated to cover a wider group of hospitalised COVID-19 positive patients, following the initial publication of the results of the RECOVERY trial. A single dose of tocilizumab should typically be considered as adjuvant treatment to dexamethasone (as standard of care) in eligible hospitalised COVID-19 patients.

The two indications are:

- oxygen saturation of <92% on room air on repeated measurement or an ongoing requirement for supplementary oxygen AND C-reactive protein level of ≥75mg/L; OR
- within 24 hours of starting respiratory support (high flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation), if an IL-6 inhibitor has not already been administered

Sarilumab continues to be recommended as a treatment option for critically ill adult patients treated with non-invasive ventilation (including high-flow nasal oxygen therapy or continuous positive airway pressure ventilation) or invasive mechanical ventilation, who have not already received tocilizumab (or other IL-6 inhibitor).

RECOVERY has now reported that in hospitalised COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved both 28-day survival (a relative reduction in mortality of 14%) and other clinical outcomes. These benefits were seen regardless of the level of respiratory support and were additional to the benefits of systemic corticosteroids, such as dexamethasone.

A finding of survival and time to recovery benefits for tocilizumab or sarilumab, over and above current standard of care (including corticosteroids), has been reported in the immune modulation therapy domain of the REMAP-CAP platform trial. Mortality was reported as 35.8% in the standard of care group, compared to 27.3% in the treatment group, an overall reduction in the relative 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.

Tocilizumab and sarilumab supply arrangements are in place to support provision under the published policies, and will continue to be carefully managed through weekly allocations at trust / health board level.

Action

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

1. **Organisations are recommended to consider prescribing a single dose of tocilizumab, as an adjuvant treatment to dexamethasone as standard of care, to eligible hospitalised patients with COVID-19 pneumonia according to the following inclusion criteria:**

    - an oxygen saturation of <92% on room air on repeated measurement or an ongoing requirement for supplementary oxygen AND C-reactive protein level of ≥75mg/L; OR
    - within 24 hours of starting respiratory support (high flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation), if an IL-6 inhibitor has not already been administered

    Please see the updated tocilizumab policy for further details.

2. **Organisations are recommended to continue to consider prescribing sarilumab to critically ill patients treated with non-invasive ventilation (including high-flow nasal oxygen therapy or continuous positive airway pressure ventilation) or invasive mechanical ventilation, who have not already received tocilizumab or other IL-6 inhibitor.** To maximise the availability of tocilizumab for the broader patient population where possible organisations are recommended to use sarilumab for the intensive care population where local supplies allow. Please see the updated sarilumab policy for further details.

3. 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.

4. Any organisation treating patients with either IL-6 inhibitor, 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.

5. In England, trusts who have not yet done so 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. Blueteq forms are also available for post pubescent children under NHS England's Medicines for Children Policy. 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.

6. Tocilizumab and sarilumab should be ordered through existing (business as usual) routes. Arrangements have been made with Roche CHUGAI and Sanofi to secure 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 hospital admission activity). Retrospective reimbursement of medicines costs will continue to be managed as usual through the excluded drugs funding route in England. HSC Trusts in Northern Ireland should work with the Regional Pharmaceutical Procurement Service to identify and record tocilizumab and sarilumab use in patients with COVID-19, with details on retrospective reimbursement to be provided by the Department of Health in due course. In Scotland, hospitals should have notified NHS National Procurement of their intention to participate and have arrangements in place to identify usage of tocilizumab and sarilumab for the management of patients with COVID-19. Details on the retrospective reimbursement arrangements will follow. Health boards in Wales should have arrangements in place to identify tocilizumab and sarilumab used in the management of patients with COVID-19. Details of how medicines costs will be reimbursed will be provided by the Welsh Government.

7. Maintain access to intravenous tocilizumab for existing (non COVID-19) indications including rheumatoid arthritis (where appropriate), certain forms of paediatric arthritis and treatment of cytokine storm (CRS) following CAR-T therapy.

8. Maintain access to subcutaneous sarilumab for existing rheumatoid arthritis patients.

9. 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 moderate to severe 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-T 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 Clinical Commissioning Policies cover off-label use of tocilizumab or 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 hospitalised patients 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.

Given the uncertainty over evidence of additional benefit as well as the need to maximise available supply, **only a single dose** should be administered.

Sarilumab should be administered as a single dose of 400mg (using 2 x 200mg pre-filled syringes) as an intravenous infusion.

The Medusa monograph for sarilumab is available here (registration / log-on required).

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).

Monitoring, tracking and follow-up

IL-6 inhibitors are immunosuppresants which can suppress C-Reactive Protein (CRP) response for up to 3 months after administration. These treatments can therefore lower the ability of the immune system to fight infections which could increase the risk of getting an infection or make any infection the patient contracts worse. It also causes prolonged depression of CRP levels, making it a less reliable marker of active infection. Monitoring of longer-term progress is recommended via recruitment of patients receiving these agents to the ISARIC-CCP study. All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) must also explicitly mention that an IL-6 inhibitor has been given and the date of administration.

It is also vital that any serious suspected adverse reactions are reported immediately using the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/.

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.