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Emergent (as yet not peer-reviewed) data from the immune modulation arm of the REMAP-CAP trial indicate sizeable positive benefits with the use of tocilizumab or sarilumab in patients admitted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.