Rapid Policy Statement

Interim Clinical Commissioning Policy: IL-6 inhibitors (tocilizumab or sarilumab) for hospitalised patients with COVID-19 (adults)

31 January 2022

Commissioning position

The proposal is: Tocilizumab is recommended to be available as a treatment option through routine commissioning for adult patients (aged 18 years and older) hospitalised with COVID-19 in accordance with the criteria set out in this document. Patients may alternatively be considered for treatment with sarilumab where tocilizumab is unavailable for this indication or cannot be used.

Evidence and policy summary

This updated UK Clinical Commissioning Policy for IL-6 inhibitors reflects the change in licence for tocilizumab, which was updated in December 2021 to include authorisation for use in the treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. This now places tocilizumab as the first-line IL-6 inhibitor for hospitalised patients with COVID-19. Patients may continue to be considered for treatment with sarilumab where tocilizumab is unavailable for this indication or cannot be used.

Evidence from the REMAP-CAP trial demonstrates a clinical benefit with the use of tocilizumab or sarilumab in patients with COVID-19 requiring organ support. In February 2021, the RECOVERY trial announced the findings of tocilizumab use in a broader hospitalised population, which indicated that tocilizumab significantly improved survival and other clinical outcomes in patients with hypoxaemia and systemic inflammation (severe COVID-19).

New evidence and guidance have since emerged to indicate the possibility of equivalence between the two IL-6 inhibitors, which is summarised below:

- Further evidence from the REMAP-CAP trial has demonstrated equivalent effects of both IL-6 inhibitors on survival and requirement for organ support (84.9% posterior probability of equivalence) .

- A prospective meta-analysis of clinical trials of IL-6 inhibitors in patients hospitalized for COVID-19 showed that they were associated with lower 28-day all-cause mortality. These results led to a strong recommendation for the use of both IL-6 inhibitors (tocilizumab and sarilumab) to treat severe and critical COVID-19 in the World Health Organisation (WHO) Therapeutics and COVID-19 Living Guideline (WHO, 2022). The guideline, which was updated in January 2022, did not recommend the use of one IL-6 inhibitor over the other.

The NICE Rapid Guideline on managing COVID-19 currently recommends the use of sarilumab for adults in hospital with COVID-19 if tocilizumab cannot be used or is unavailable. These guidelines were developed based on the consensus of a separate expert group and an independent evidence summary which states there is significant uncertainty around the efficacy and safety of sarilumab compared to standard care in treating patients with COVID-19.

Implementation

Eligibility criteria

Patients must meet all the eligibility criteria and none of the exclusion criteria. Hospitalised patients are eligible[1] to be considered for **tocilizumab** if:

- COVID-19 infection is confirmed by microbiological testing or where a multidisciplinary team has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis;

  AND

- They have not already been treated during this episode with tocilizumab or sarilumab;

  AND

- Receiving dexamethasone or an equivalent corticosteroid[2] (corticosteroid CAS alert) unless contraindicated;

  AND

  Either

  - Hypoxaemia with evidence of inflammation but not yet critically ill requiring respiratory support[3] defined as:

    - C-reactive protein level of at least 75mg/L; AND
    - an oxygen saturation of <92% on room air OR requirement for supplemental oxygen;

[1] The decision to initiate treatment with tocilizumab or sarilumab should be made by the receiving consultant and with the support from multi-disciplinary colleagues in cases of uncertainty

[2] Patients are expected to be on a corticosteroid as the current standard of care, except where there is a strong contraindication against its use. Patients may be commenced on both a corticosteroid and tocilizumab simultaneously if deemed clinically appropriate.

[3] In the context of the COVID-19 pandemic, treatment of patients critically unwell with COVID-19 can be in the following (critical care equivalent) settings: designated intensive care unit (ICU); surge ICU; or other hospital settings delivering an equivalent level of respiratory care (such as respiratory ward, infectious disease ward).

Or

- In the early stages of critical illness requiring respiratory support (if an IL-6-inhibitor has not been already administered for COVID-19) defined as:
    - Within 48 hours[4] of commencement of respiratory support (high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation), regardless of C-reactive protein level.

Sarilumab should be considered as an alternative option if tocilizumab is unavailable for this indication or cannot be used, and the above criteria are met.

Exclusion criteria and cautions

Tocilizumab should not be administered in the following circumstances:

- Known hypersensitivity to tocilizumab
- Liver enzymes [alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] more than ten times the upper limit of normal
- Absolute neutrophil count of less than 1 x 10^9/L
- Platelet count of less than 50 x 10^3/µL

Sarilumab should not be administered in the following circumstances:

- Known hypersensitivity to sarilumab
- Liver enzymes [alanine aminotransferase (ALT) or aspartate aminotransferase (AST)] more than 5 times the upper limit of normal
- A baseline platelet count of less than 150 x 10^9/L

Please refer to the Summary of Product Characteristics (SmPC) for tocilizumab and sarilumab (in Northern Ireland, refer to the EMA SmPCs for tocilizumab and sarilumab) for special warnings and precautions for use, although some may not be relevant for use in the acute setting, as the licensed indications address long-term use.

Caution should be exercised when considering treatment with IL-6 inhibitors in the following circumstances:

- Co-existing infection[5] that might be worsened by IL-6 inhibitor therapy
- A pre-existing condition or treatment resulting in ongoing immunosuppression

Caution is also necessary when prescribing IL-6 inhibitors to patients with neutropenia or thrombocytopenia. Please note that C-reactive protein (CRP) levels may be depressed for some time after treatment with tocilizumab.

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[4] Treatment should be started as early as possible

[5] 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.

Pregnancy and women of childbearing potential

Tocilizumab and sarilumab should not be used during pregnancy unless clinically necessary.

The SmPC for tocilizumab currently states that: "*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. RoActemra should not be used during pregnancy unless clearly necessary."*

The SmPC for sarilumab currently states that: *"Women of childbearing potential should use effective contraception during and up to 3 months after treatment. There are no or limited amount of data from the use of sarilumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Kevzara should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab."*

The SmPC for tocilizumab and sarilumab should be consulted if further information is required.

For women who are breast-feeding, the SmPCs for both tocilizumab and sarilumab state: *"It is unknown whether tocilizumab/sarilumab is excreted in human breast milk. The excretion of tocilizumab/sarilumab in milk has not been studied in animals. A decision on whether to discontinue breast-feeding or to discontinue IL-6 inhibitor therapy should be made taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman."*

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[6].

A single dose is to be administered. A second dose should not be considered, given the uncertainty over evidence of additional benefit as well as the need to maximise available supply. 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. For a 400mg dose two 200mg pre-filled syringes should be injected into a 100mL sodium chloride 0.9% infusion bag. The bag should be inverted at least 10 times to ensure thorough mixing and given over 1 hour[7].

[6] The following infusion rate is recommended: 10ml/hour for first 15 minutes then 130ml/hour for the remaining 45 minutes followed by a 20ml normal saline flush.

[7] The following infusion rate is recommended: 10ml/hour for first 15 minutes then 130ml/hour for the remaining 45 minutes followed by a 20ml normal saline flush

Sarilumab should not be infused concomitantly in the same IV line with other medications**.** Further information on the use of sarilumab intravenously is available at: https://medusa.wales.nhs.uk/ (registration may be required).

Co-administration

There is no interaction expected between IL-6 inhibitors with other commissioned COVID-19 treatments. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Please refer to other published UK clinical commissioning policies setting out available COVID-19 treatments here.

Safety reporting

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

In addition, treatment with IL-6 inhibitors can lower the ability of the immune system to fight infections. This could increase the risk of getting a new infection or make any infection the patient contracts worse. It also causes prolonged depression of CRP levels, making CRP a less reliable marker of active infection. 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 explicitly mention that an IL-6 inhibitor has been given and the date of administration. Clinicians must ensure the GP is aware the patient has received an IL-6 inhibitor and provide information to the patient to such effect.

Marketing authorisation

Tocilizumab

Tocilizumab delivered intravenously is authorised for use in the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. It is also licensed 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

Sarilumab has marketing authorisation for subcutaneous use in adults with moderate to severe active rheumatoid arthritis. **The use of sarilumab intravenously 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 policy will be in effect from the date of publication.

Policy review date

This is an interim rapid clinical policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. This policy may need amendment and updating if, for instance, new trial data emerges, supply of the drug changes, or a new evidence review is required. A NICE Technology Appraisal or Scottish Medicines Consortium (SMC) Health Technology Assessment or All Wales Medicines Strategy Group (AWMSG) appraisal of tocilizumab for COVID-19 would supersede this policy when completed.

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.

Definitions

COVID-19	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus
High-flow nasal cannula	An oxygen supply system capable of delivering up to 100% humidified and heated oxygen at a flow rate of up to 60L/minute
Continuous positive airway pressure	A type of positive airway pressure in which air flow is introduced into the airways to maintain a continuous pressure that constantly keeps the airways open
Non-invasive ventilation	The administration of breathing support for those unable to breathe on their own without using an invasive artificial airway
Invasive mechanical ventilation	A life support treatment which helps people breathe using an invasive artificial airway when they are not able to breathe enough on their own

References

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2. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. doi:10.1016/S0140-6736(21)00676-0
3. REMAP-CAP Investigators, Derde LPG, et al. Effectiveness of Tocilizumab, Sarilumab, and Anakinra for critically ill patients with COVID-19 The REMAP-CAP COVID-19 Immune Modulation Therapy Domain Randomized Clinical Trial. 2021. Preprint available at: https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2
4. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med*. 2021;384(16):1491-1502. doi:10.1056/NEJMoa2100433
5. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, Vale CL, et al. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. *JAMA*. 2021;326(6):499-518. doi:10.1001/jama.2021.11330