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Position Statement: Use of investigational immunomodulatory agents for COVID-19 in adults

Interim Support for hospital clinicians in England

Document management

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Document control

Date	Version	Amendments
22 April 2020	1.0	New document

Contents

Abbreviations

Abbreviation	Meaning
CMO	Chief Medical Officer
NIHR	National Institute for Health Research
R&D	Research and Development
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
sHLH	Secondary haemophagocytic lymphohistocytosis
SoC	Standard of Care

Key messages

- A subset of patients with COVID-19 may experience an exaggerated hyperinflammatory response
- COVID-19 associated hyperinflammation predominantly involves the lung however may progress to secondary haemophagocytic lymphohistocytosis (sHLH) which is a systemic and multi-organ condition
- The optimal treatment for COVID-19 associated hyperinflammation is unknown and trials are needed
- Patients who meet diagnostic criteria for sHLH should be managed within established pathways, guided by a specialist familiar with hyperinflammation

1. Introduction

1.1. A subset of patients with COVID-19 experience an exaggerated host hyperinflammatory response associated with hypercytokinaemia[1,2], following or associated with the initial viral response phase[1].

1.2. Terminology regarding hyperinflammation is heterogeneous however 'hyperinflammation' is generally considered an umbrella term for a number of syndromes associated with severe systemic macrophage activation (Figure 1). The most prevalent is secondary haemophagocytic lymphohistocytosis (sHLH) which is a systemic and multi-organ condition. This manifests as organomegaly, cytopenias and liver function derangement.

1.3. Hyperinflammation in the context of COVID-19 predominantly involves the lung without the systemic effects of sHLH. However, COVID-19 associated hyperinflammation can progress to multi-organ disease characteristic of sHLH.[3] Current knowledge describing differences between hyperinflammation in the context of COVID-19 and sHLH is available https://www.ncbi.nlm.nih.gov/pubmed/32251717.

1.4. The optimal treatment strategy for COVID-19 associated hyperinflammation is unknown. Immunomodulation is not a specific therapy for the coronavirus (SARS-Cov-2) that causes COVID-19 however it is hypothesised that immunomodulatory agents may prevent or limit clinical deterioration in COVID-19, in a subgroup of patients with associated hyperinflammation.[4] It is unknown whether potential benefit of immunomodulation outweighs any potential risks.[5]

1.5. Of note, if individuals progress to and meet the diagnostic criteria for sHLH (e.g. H-Score, HLH 2004 criteria), treatment should follow pre-defined guidance available locally, which ideally should involve input from a specialist familiar with hyperinflammation.

1.6. Clinical trials are being designed to explore the risk:benefit ratio of immunomodulatory agents that target the proinflammatory cytokine pathways implicated in COVID-19 associated hyperinflammation. Examples include inhibiting IL-1 (anakinra and canakinumab), IL-6 (tocilizumab, siltuximab & sarilumab), Bruton's tyrosine kinase (BTK) pathway (acalabrutinib) and the JAK-STAT pathway (ruxolitinib).

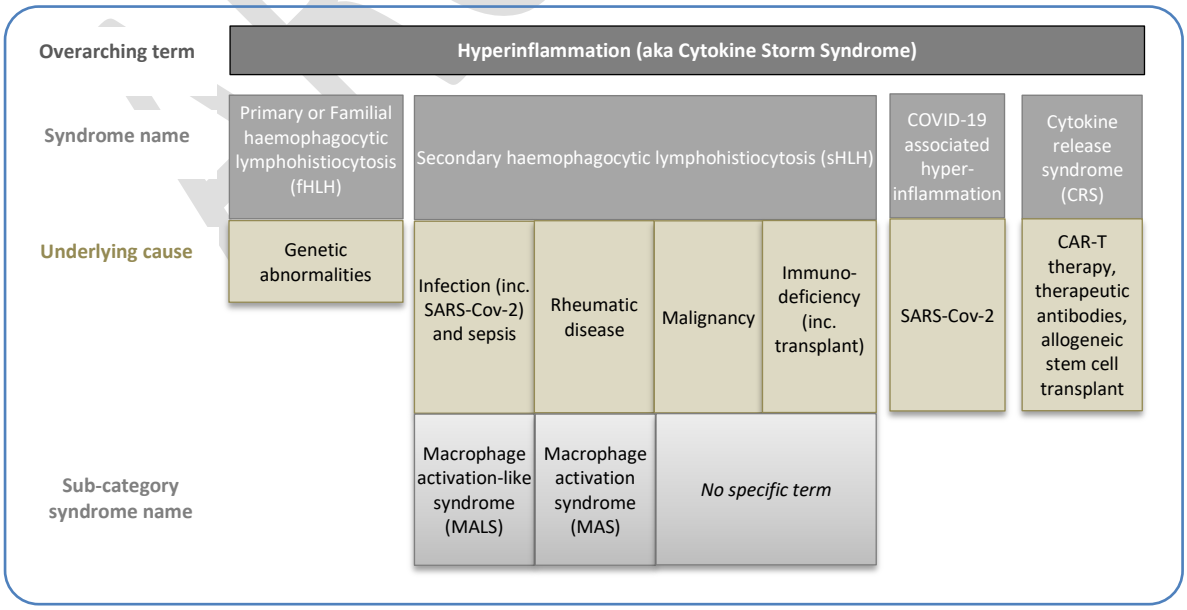

Figure 1: Terminology associated with hyperinflammation (note that variation exists in the literature)

2. Aim

2.1. This position statement for acute Provider clinicians provides interim supporting information on the appropriate use of investigational immunomodulatory agents in the management of adults with COVID-19 associated hyperinflammation. This interim position statement will be updated in response to relevant national developments and superseded when specific guidance is published by NHS England, Department of Health and Social Care, Public Health England or the National Institute for Health and Care Excellence.

2.2. Information contained within this position statement does not represent a 'recommendation', however it is intended to provide support to healthcare professionals when considering available treatment options in specific patients with COVID-19 where hyperinflammation warrants the consideration of immunomodulation.

3. Interim supporting information

3.1. There are no licenced immunomodulatory therapies to treat COVID-19 associated hyperinflammation. The standard of care in managing COVID-19 associated hyperinflammation is yet to be defined. Randomised controlled trials to address this are ongoing.

3.2. Several investigative immunomodulatory agents have potential to be repurposed for the management of COVID-19 associated hyperinflammation (including and not limited to anakinra, interferon-beta, tocilizumab, sarilumab, canakinumab and ruxolitinitib); the evidence-base for these agents is summarised in Appendix 1.

3.3. It is recognised that access to clinical trials offering immunomodulatory options may not be available at all sites at the point of patient need. However, as far as possible, investigative agents should be used in the context of a clinical trial[a] using supplies allocated for clinical trial use (e.g. via trial sponsor or Public Health England). The off-label use (aka 'non-trial' or 'compassionate-access' use) of medicines should be avoided because:

- Medicines currently available within the NHS supply chain are needed for the patients already prescribed within licensed indications[6]
- Medicines supplies are limited therefore their use outside the context of a clinical trial may compromise the feasibility of required trials.

3.4. As relevant trials of investigative immunomodulatory agents open, hospitals managing COVID-19 cases are encouraged to engage with their R&D services and establish capacity to recruit into those trials – refer to Section 4.

3.5. The following interventional hospital-only trials (including an immunomodulatory agent) are urgent public health research studies for COVID-19:

- RECOVERY (in hospital trial; UK study open to all Trusts) added a second randomisation for patients with progressive disease and evidence of hyperinflammation; it is endorsed by NHS England[b] and the Chief Medical Officer (CMO)[c]
- REMAP-CAP (critical care trial; international with UK sites) added immunomodulatory and anti-viral domains for COVID-19; it is endorsed by the CMO
- COVACTA (in hospital trial; international with UK sites)

3.6. The following observational studies are strongly encouraged for any patient, including those receiving investigational agents in trials (co-recruitment into observational studies does not preclude enrolment into a clinical trial of investigative medicinal products):

- ISARIC-CCP (confirmed COVID-19)
- ISARIC-GenOMICC (suspected or confirmed COVID-19 in critical care)

3.7. It should be noted that existing pathways for patients who meet the diagnostic criteria for sHLH (e.g. H-score, HLH 2004 criteria) are not affected by these recommendations.

3.8. Immunomodulation is not considered a specific therapy for SARS-Cov-2 that causes COVID-19. Supporting information for the use of investigational antiviral agents for SARS-Cov-2 (including remdesivir, ritonavir/lopinavir, hydroxychloroquine, chloroquine, azithromycin and interferon-beta) is available at https://ctag-support.org.uk/docs/antivirals.pdf

[a] Chief Medical Officers strongly discourage the use of off-licence treatments outside of a trial, where participation in a trial is possible

[b] NHS England & NHS Improvement suggest Trusts consider enrolling patients into UK clinical trials, including the RECOVERY trial[7]

[c] Chief Medical Officers have specified PRINICPLE, RECOVERY and REMAP-CAP are key national trials and strongly discourage the use of off-licence treatments outside of a trial, where participation in a trial is possible[8]

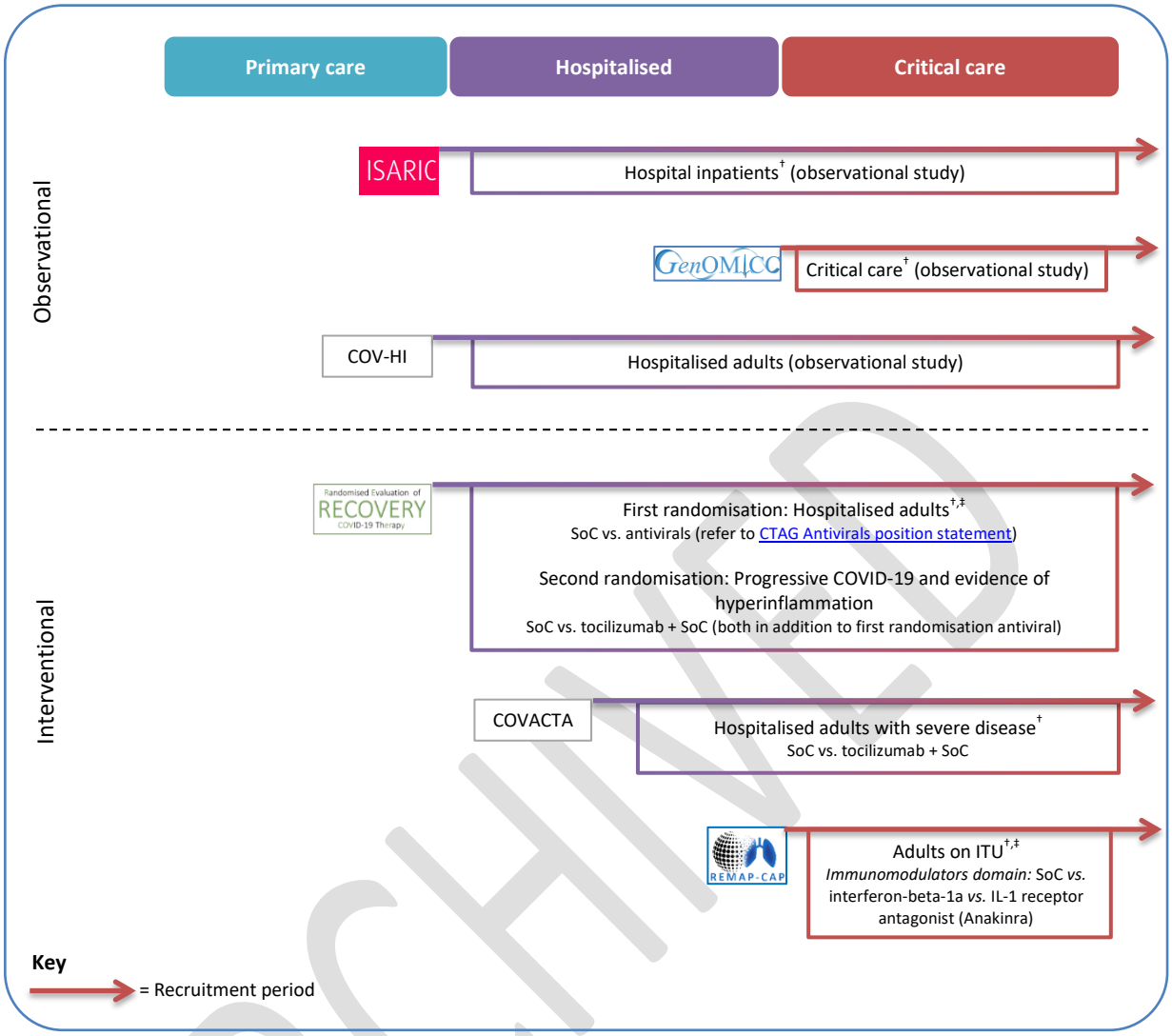

Figure 2: Immunomodulatory components for recruiting UK Clinical Studies as at 16 April 2020. Participation for COVID-19 trials will be through adoption at local sites, information should be available through local Research and Development Offices. SoC; standard of care. † Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/. ‡ These studies also include domains which are outside the scope of this document (e.g. antivirals, ventilation strategies).

4. UK clinical studies

4.1. The Chief Medical Officer for England has written to Trusts to ask that every effort is made to enrol COVID-19 patients into national priority clinical trials and that the use of off-licence treatments outside of a trial is strongly discouraged, where participation in a trial is possible[2].

4.2. The NIHR is working with the Department of Health and Social Care to coordinate the national research agenda[3].

4.3. Organisations should prioritise support for studies which have been nationally prioritised and pause any local studies that impede their ability to contribute to national research efforts[3].

4.4. A complete list of nationally prioritised research studies for COVID-19 is available on the NIHR website https://www.nihr.ac.uk/covid-19/urgent-public-health-studies-covid-19.htm

4.5. Immunomodulatory interventional studies and observational studies of relevance to COVID-19 associated hyperinflammation are summarised below:

- Table 1: Recruiting trials
- Table 2: Proposed trials

Table 1: Recruiting in the UK – Immunomodulatory interventional clinical trials and observational studies

Status		Trial	Population	Specific to hyperinflammation?	Intervention arms
Recruiting	Observational	ISARIC-CCP† (International study)	Hospital inpatients; confirmed COVID-19	NA	N/A – study has multiple objectives (see protocol); including describing clinical features and response to treatments. Case Record Forms (CRF) are available.
		ISARIC-GenOMICC† (International study)	Critical care; confirmed or suspected COVID-19	NA	N/A – study designed to identify host genetic variants underlying susceptibility to severe adverse outcomes.
		COV-HI (UK study with limited UK sites)	Hospital inpatients; adults with confirmed COVID-19	NA	N/A – study designed to understand which patients are more likely to develop hyperinflammation associated with COVID-19.
	Interventional	RECOVERY†,‡ (UK study open to all Trusts)	First randomisation: Hospital inpatients; adults with suspected or confirmed COVID-19 Second randomisation: Progressive COVID-19 (SpO2 <92% on room air or requiring oxygen) and CRP ≥75 mg/L	First randomisation: No Second randomisation: Yes CRP ≥75 mg/L	First randomisation: SoC vs. antivirals (refer to CTAG Antivirals position statement) Second randomisation: – SoC – Tocilizumab + SoC (both in addition to first randomisation antiviral)
		REMAP-CAP†,‡ (International study with UK sites)	Critical care; adults with suspected or confirmed COVID-19	No	Immunomodulatory domains for COVID-19: – SoC – Interferon-beta-1a – Anakinra Note: An amendment is planned to include tocilizumab and sarilumab
		COVACTA†: A study to evaluate tocilizumab in patients with severe COVID-19 pneumonia (International study with UK sites)	Hospital inpatients; adults with confirmed COVID-19 (severe disease; SpO2 ≤ 93% on room air or PaO2/FiO2 <300 mmHg)	No	– SoC – Tocilizumab + SoC

† Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/. ‡ These studies also include domains which are outside the scope of this document (e.g. antivirals, ventilation strategies).

Table 2: Proposed in the UK – Immunomodulatory interventional clinical trials and observational studies

Status		Trial	Population	Specific to hyperinflammation?	Intervention arms
Proposed	Observational	COVID19_BMT (UK study, multicentre)	Allogeneic stem cell transplant recipients with COVID-19	Yes	N/A
		REACT (International study with UK sites)	Hospital patients treated with anti-cytokine therapy for COVID-19	Yes Fever, CRP	N/A
	Interventional	CANCOVID† (International study with UK sites)	Hospital inpatients; adults with confirmed COVID-19 (severe disease; SpO2 ≤ 93% on room air or PaO2/FiO2 <300 mmHg) and evidence of cytokine release syndrome	Yes ○ CRP ≥20 mg/L or ferritin level ≥600 µg/L	– Placebo + SoC – Canakinumab + SoC ○ Note: All patients to receive SOC per local practice for COVID-19-induced pneumonia; SOC may include anti-viral treatment, corticosteroid and/or supportive care.
		RUXCOVID† (International study with UK sites)	Hospital inpatients; patients ≥ 12 years with confirmed COVID-19 (severe disease; respiratory frequency ≥ 30/min or SpO2 ≤ 93% on room air or PaO2/FiO2 <300 mmHg)	No	– Placebo + SoC – Ruxolitinitib + SoC Note: All patients to receive SoC per local practice for COVID-19-induced pneumonia.
		DECISIVE (UK study, multicentre)	Hospital inpatients; adults with severe COVID-19 and hyperinflammation	Yes	– Tocilizumab + SoC – Anakinra + SoC – SoC only Note: adaptive design may permit addition of other immunomodulator arms
		TOCIVID (International Phase II study)	Hospital inpatients; adults with confirmed COVID-19 (severe disease; SpO2 ≤ 93% on room air or requiring supplemental oxygen)	No	Single arm study: Tocilizumab + SoC

† Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/

5. References

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6. Membership and provenance

Support within this document is provided by the COVID-19 Therapeutics Advice & Support Group (CTAG) immunomodulatory subgroup.

The provenance for this subgroup is the HLH Across Speciality Collaboration (HASC).

Appendix 1: Publications for investigational immunomodulatory agents to treat hyperinflammation associated with COVID-19

The Cochrane database of Covid-19 studies was searched to identify the current evidence-base for COVID-19 (Drugs Searched: tocilizumab; sarilumab; anakinra; ruxolitinib; siltuximab):

- Randomised controlled trials https://covid-nma.com/living_data/index.php
- Non-randomised controlled trials https://covid-nma.com/pharmacologic-treatments/

Table A1: Published Research

Reference	Study Type	Sample Size	Method/Drug	Country	Link
Xun X, *ChinaXiv*[†], 2020	Case Series Report	21	**Tocilizumab** (400 mg administered one time/administered two times to 3 patients) plus standard care	China	Link
Luo P, *J Med Virol*, 2020	Retrospective Cohort	15	**Tocilizumab** (one to three doses of 80 -600 mg, administered over 7 days), plus **methylprednisolone** (40-400 mg /OD or BD, administered to 8/15 patients for 4-6 days)	China	Link
Gritti G, medRxiv[†], 2020	Case Series Report	21	**Siltuximab** (one to two doses of 11 mg/kg/day over one hour)	Italy	Link

[†]Not peer reviewed

Disclaimer

Due to the urgency for interim guidance, only a limited number of agents have been assessed and a wholly systematic approach to assessing the evidence (such as GRADE) has not been performed. Some subjective judgments are solely the consensus opinion of the authors and consulted experts