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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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Version number:	1.1
Available on:	https://www.ctag-support.org.uk/immunomodulators
Publication date:	07 May 2020
Review date:	This document will be continuously reviewed. If you identify any information that needs to be updated please contact admin.ncl-mon@nhs.uk.

Document control

Date	Version	Amendments
22 April 2020	1.0	New document
07 May 2020	1.1	Updated evidence summaries in Appendix 1.

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 and sarilumab), Bruton's tyrosine kinase (BTK) pathway (acalabrutinib),JAK-STAT pathway (ruxolitinib) and dipeptidyl peptidase 1 (DPP1) inhibitors (brensocatib).

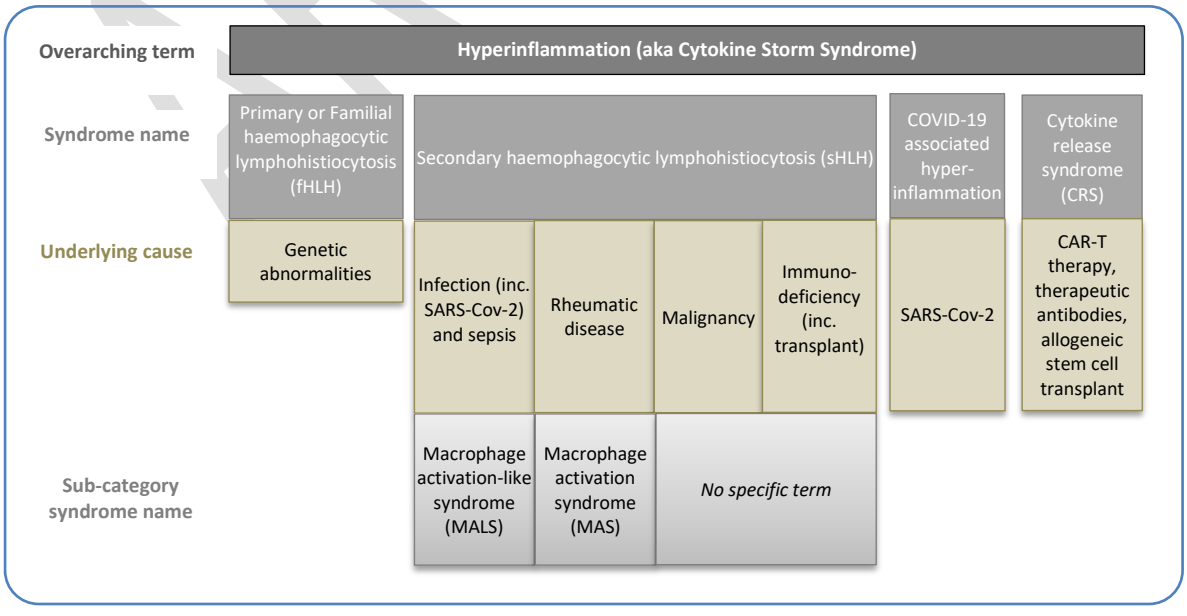

Figure 1: Terminology associated with hyperinflammation (note that variation exists in the literature)

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 ruxolitinib); 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 hospital-only trials for investigative immunomodulatory agents 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://www.ctag-support.org.uk/antivirals. Be aware that recruitment into one trial (e.g. of investigative antivirals) does not necessarily preclude recruitment into another (e.g. of investigative immunomodulators).

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[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]

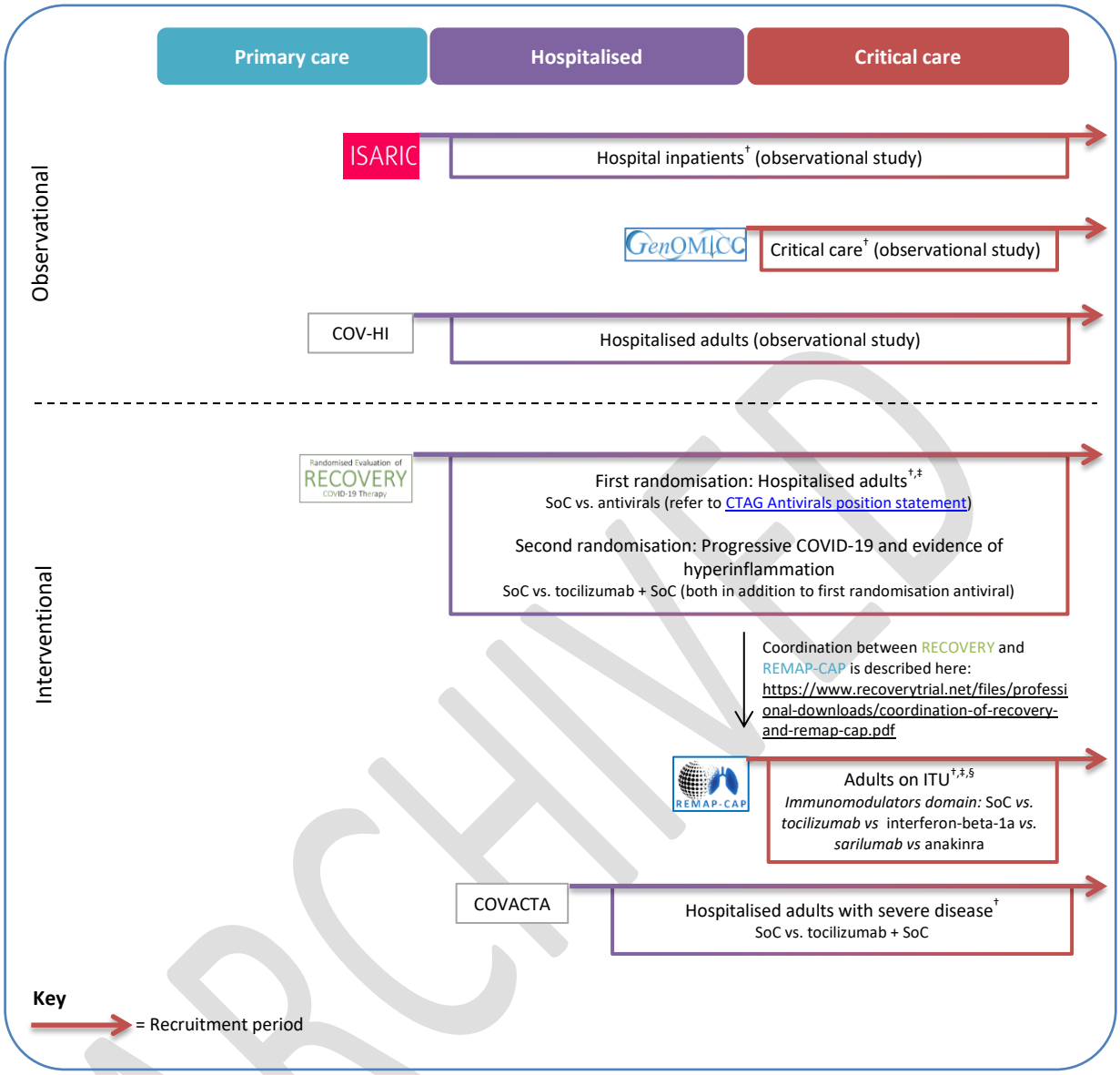

Figure 2: Immunomodulatory components for recruiting UK Clinical Studies as at 16 April 2020. Participation for COVID-19 trials will be through adoption at local sites, information should be available through local Research and Development Offices. SoC; standard of care. † Nationally prioritised research 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). § Tocilizumab is currently an intervention active at some sites; sarilumab, interferon-beta-1a and anakinra will be available to sites shortly.

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 studies
- Table 2: Proposed studies

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) (NCT04262921)	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.
		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) (ISRCTN50189673)	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) (NCT02735707)	Critical care; adults with suspected or confirmed COVID-19	No	Immunomodulatory domains for COVID-19: – SoC – Tocilizumab – Interferon-beta-1a – Anakinra – Sarilumab
		COVACTA† (International study with UK sites) (NCT04320615)	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). § Tocilizumab is currently an intervention active at some sites; sarilumab, interferon-beta-1a and anakinra will be available to sites shortly.

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) (NCT04349540)	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) (NCT04362813)	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) (NCT04362137)	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 – Ruxolitinib + 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) (NCT04317092)	Hospital inpatients; adults with confirmed COVID-19 (severe disease; SpO2 ≤ 93% on room air or requiring supplemental oxygen)	No	Single arm study: Tocilizumab + SoC

Status	Trial		Population	Specific to hyperinflammation?	Intervention arms
		STOP-COVID19 (in setup, pending Health Research Authority approval)	Awaiting further information	Awaiting further information	- Brensocatib + SoC - Placebo + SoC Awaiting further information

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

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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 NIHR list of nationally prioritised studies was searched to identify novel treatments for 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, brensocatib):

- Randomised controlled trials https://covid-nma.com/living_data/index.php
- Observational studies https://covid-nma.com/observational_studies/

Table A1: Evidence base for specific therapies for SARS-CoV-2 infection: Inadequate data to recommend compassionate use, await further data

Therapy	Data: Other forms of hyperinflammation	Data: SARS-CoV-2 induced hyperinflammation	Safety profile	UK feasibility
Anakinra	IL-1 specific inhibitor used off-label to treat HLH and approved for this indication at several NHS Trusts in the UK. It is licensed to treat Still's disease (including systemic juvenile idiopathic arthritis and Adult-Onset Still's disease), which is recognized in progressing to hyperinflammation.[1,2] In a double-blind RCT in 893 sepsis patients, anakinra did not lengthen survival time compared to placebo however two post-hoc analyses found survival benefit in patients with '≥1 organ dysfunction'[3] or 'disseminated intravascular coagulation and hepatobiliary dysfunction'[4] (features suggestive of sHLH). It is unknown whether these data apply to patients with sHLH due to the post-hoc analysis (risk of Type 1 error) and the absence of prospectively confirmed sHLH diagnosis. Multiple case-series[5–8] find a high proportion of patients with sHLH treated with anakinra survive. These reports were limited by the lack of a control arm, and small number of patients.	No results yet reported.	In the study on sepsis patients, the single serious adverse event reported more commonly in anakinra patients versus placebo was cardiopulmonary arrest 11% versus 8%), with similar numbers in each group thought to be related to anakinra or placebo. The authors of the post-hoc analysis stated that this trial and others that investigated anakinra did not find an increased mortality rate or serious/non-serious reactions versus placebo.	An active interventional arm in the REMAP-CAP trial. Proposed as an interventional arm in the DECISIVE trial.

Therapy	Data: Other forms of hyperinflammation	Data: SARS-CoV-2 induced hyperinflammation	Safety profile	UK feasibility
Tocilizumab	Tocilizumab binds to both soluble and membrane bound interleukin-6 receptors, and is licensed following demonstration of efficacy in treating CRS associated with the CAR-T therapies such as tisagenlecleucel and axicabtagene ciloleucel.[9] As part of clinical trials for CAR-T therapy, tocilizumab was included in the protocol to treat CAR-T induced CRS. Co-medication with corticosteroids was allowed and no comparative data were available at the time of licensing; however, rapid effects on objective early endpoints (e.g. vital signs) provided sufficient evidence for the role of tocilizumab in the resolution of a life-threatening condition with a previously unmet need.	A case series report in severe or critical COVID-19 infection in China[10] found 15/20 patients (75%) given tocilizumab had lowered oxygen requirements and one patient needed no further oxygen therapy; lung lesions improved in 19 patients (90.5%) and 19 patients were discharged (90.5%), including two patients from critical care. All patients also received standard of care which included lopinavir and methylprednisolone. However, no control arm was included and only a small number of participants was used. This publication was not peer reviewed. A case series in China treated 15 patients with tocilizumab.[11] Eight patients were also given methylprednisolone. The study describes the kinetics of CRP and IL-6 changes following tocilizumab administration. One patient demonstrated clinical improvement, nine patients stabilised, two demonstrated disease aggravation and three patients died. This study was limited by the lack of a control arm, short follow-up and small number of patients. A press release suggests the results from the French CORIMUNO-TOCI study of 129 patients[12] show a significantly lower proportion of patients reaching the primary composite outcome (requirement for ventilation or death by day 14) among those receiving tocilizumab and standard of care versus standard of care alone. A publication in a peer-reviewed journal is awaited.	The marketing authorization holder for tocilizumab was asked to supply further data on safety in CAR-T induced CRS due to low numbers of patients exposed to higher doses. No adverse events were reported in the case series and the retrospective cohort study did not report on safety.	An interventional arm of the REMAP-CAP, RECOVERY and COVACTA trials. Proposal as an interventional arm to the planned DECISIVE trial.

Therapy	Data: Other forms of hyperinflammation	Data: SARS-CoV-2 induced hyperinflammation	Safety profile	UK feasibility
Sarilumab	Sarilumab binds to both soluble and membrane bound interleukin-6 receptors, preventing IL-6 mediated signaling. It is licensed in the treatment of moderate to severe rheumatoid arthritis.[13] No evidence in the form of a clinical study could be identified to demonstrate the efficacy of sarilumab in treating patients suffering from other hyperinflammatory states.	A press release suggests that results from the Phase 2 portion of the US Phase 2/3 study (NCT04315298)[14] shows sarilumab lowers CRP, compared to placebo. A "pre-specified exploratory analysis" of patients with 'severe' disease (requiring oxygen supplementation without mechanical or high-flow oxygenation) and 'critical' disease (requiring mechanical ventilation or high-flow oxygenation or required treatment in an intensive care unit) found sarilumab had no benefit on clinical outcomes. Further analysis found negative trends for most outcomes in the 'severe' group and positive trends for the 'critical' group. The Phase 3 portion of the US trial was subsequently amended to enrol 'critical' patients only. A publication in a peer-reviewed journal is awaited.	No safety data has been reported in the COVID-19 population.	Proposal to add as an interventional arm to the RECOVERY trial. An interventional treatment arm in the REMAP-CAP trial.
Canakinumab	Canakinumab binds with interleukin-1 beta to prevent its inflammatory activity. It is licensed to treat Still's disease (including systemic juvenile idiopathic arthritis and Adult-Onset Still's disease), which is recognized in progressing to hyperinflammation. No evidence in the form of a clinical study could be identified to demonstrate the efficacy of canakinumab in treating patients suffering from other hyperinflammatory states.	No results yet reported.	No safety data has been reported in the COVID-19 population.	Proposed as an interventional treatment in CANCOVID

Therapy	Data: Other forms of hyperinflammation	Data: SARS-CoV-2 induced hyperinflammation	Safety profile	UK feasibility
Ruxolitinib	Ruxolitinib is a selective Janus-associated kinase (JAK) 1 and 2 inhibitor responsible for cytokine signaling. Ruxolitinib is licensed for myelofibrosis and thrombocythaemia. A case report in which a patient was given ruxolitinib for sHLH refractory to standard of care therapy[15] (including IVIG, dexamethasone, etoposide and rituximab) describes an improvement in biomarkers (except no resolution of pancytopaenia), though still ultimately led to death. An open-label pilot trial in five sHLH patients found resolution of symptoms and disease-related laboratory abnormalities following treatment with 15mg twice daily of ruxolitinib. This study had a long follow-up period but is limited by the open-label single arm design and only five participants.[16] A further case series described the efficacy of ruxolitinib in two patients meeting criteria for sHLH refractory to other treatments. Due to being a case series, it is limited by the study design.[17]	No results yet reported.	In the open-label trial, six adverse events were classified as a possible or probable consequence of ruxolitinib. One was a serious adverse event (febrile neutropaenia) and one grade two adverse event of pain in extremity caused discontinuation.	Proposed as an interventional treatment in RUXCOVID
Siltuximab	Siltuximab binds with interleukin-6 to prevent binding with soluble and membrane-bound IL-6 receptors. It is licensed in the UK to treat Castleman's disease.[18] No evidence in the form of a clinical study could be identified to demonstrate the efficacy of siltuximab in treating patients suffering from other hyperinflammatory states.	A case series in 21 patients in Italy[19] reports reduced CRP in 16 patients, with an improvement in clinical condition in 7 patients (33%), stabilisation with no worsening in 9 patients (43%) and 5 patients experienced a worsening in condition including one patient who died (24%). This publication was not peer reviewed. This study did not have a control arm and the low number of patients were followed up for 8 days.	Of the patients that deteriorated in the SARS-CoV-2 case series, one suffered a cerebrovascular event.	Not available under a clinical trial in the UK currently

Therapy	Data: Other forms of hyperinflammation	Data: SARS-CoV-2 induced hyperinflammation	Safety profile	UK feasibility
Brensocatib	Brensocatib is a selective reversible inhibitor of dipeptidyl peptidase 1 (DPP1), an enzyme that activates neutrophil serine proteases during neutrophil maturation in the bone marrow. Neutrophils play an important role in lung inflammation including in ARDS.[20] Brensocatib has recently completed a phase 2 trial in patients with non-cystic fibrosis bronchiectasis (preliminary results reported by the company indicate success though is not published). It has not been investigated for any other indication.[21]	No results yet reported.	The only data on safety is from a company press release as phase 2 trial data has not yet been published. The common adverse effects seen in patients taking brensocatib was cough, headache, sputum increase, dyspnea, fatigue, and upper respiratory tract infection.	Proposed as an intervention treatment in the STOP-COVID19 trial.

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

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