Royal College of Physicians

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Position Statement:
Use of investigational immunomodulatory medicines for COVID-19

Interim support for UK hospital clinicians

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In partnership with

Advice & Support Group partners

Royal College of Physicians Joint Specialty Committee for Infectious Disease (lead partner)
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Document management

This document will be continuously reviewed. If you identify any information that needs to be updated please contact admin.ncl-mon@nhs.uk.

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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
ECMO	Extracorporeal membrane oxygenation
IVIG	Intravenous Immunoglobulin
PIMS-TS	Paediatric Inflammatory Multisystem Syndrome – Temporarily associated with SARS-CoV-2
WHO	World Health Organisation

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 with significant morbidity and mortality
- CTAG strongly recommends systemic corticosteroids for patients who fit definitions of WHO-defined severe or critical COVID-19, or in patients who otherwise have a new oxygen requirement
- CTAG also recommends **not to use** corticosteroid therapy in patients with WHO-defined non-severe COVID-19 (i.e. the absence of any signs of severe or critical COVID-19).
- As far as possible, the use of investigative immunomodulatory medicines should be used in the context of a national priority clinical trial. This includes patients treated with remdesivir +/- corticosteroids
- Patients who meet diagnostic criteria for sHLH should be managed within established pathways, guided by a specialist familiar with hyperinflammation
- IVIG for PIMS-TS should ideally be used within the context of the RECOVERY clinical trial
- Advice on the appropriate use of remdesivir is available at https://www.ctag-support.org.uk/antivirals
- Suspected side effects to medicines used in coronavirus treatment should be reported via the Yellow Card COVID-19 reporting site: https://coronavirus-yellowcard.mhra.gov.uk

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. A final common pathway amongst hyperinflammatory syndromes include multiple organ dysfunction syndrome and death.

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. A significant systemic inflammatory response has also been recognised in a small number of paediatric cases; 'paediatric multisystem inflammatory syndrome' has been associated with COVID-19 infection. Certain research registries and trials are including paediatric patients.[4]

1.5. 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 medicines may prevent or limit clinical deterioration in COVID-19, in a subgroup of patients with associated hyperinflammation.[5]

1.6. 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.

1.7. Clinical trials are being designed to explore the risk:benefit ratio of immunomodulatory medicines that target the proinflammatory cytokine pathways implicated in COVID-19 associated hyperinflammation.

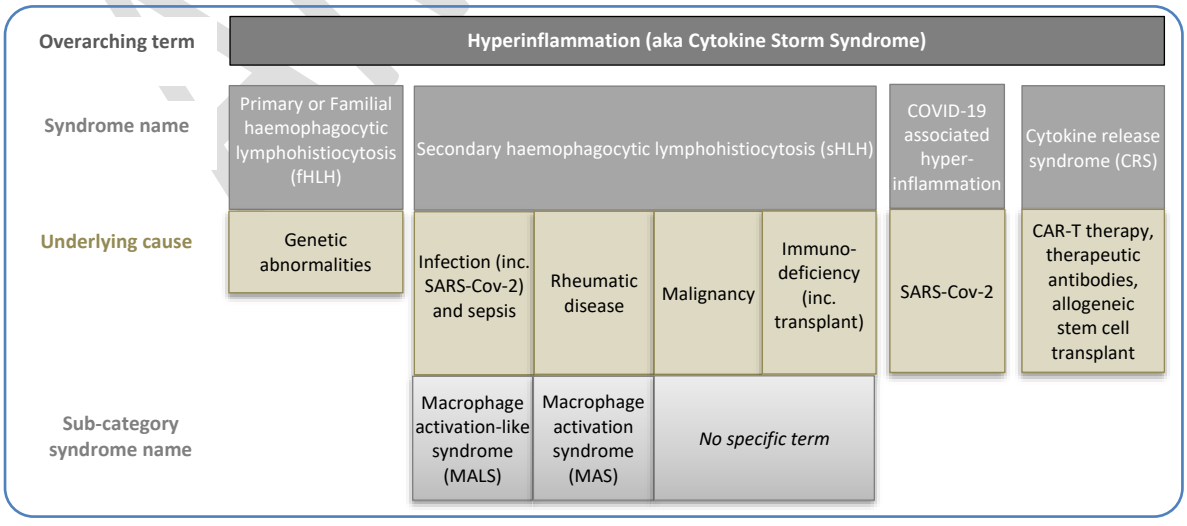

Figure 1: Terminology associated with hyperinflammation (note that variation exists in the literature)

2. Aim

2.1. To provide interim supporting information on the appropriate use of investigational immunomodulatory medicines in the management of COVID-19 associated hyperinflammation. This position statement will be updated in response to national developments and superseded when specific guidance is published by UK health technology assessment bodies (e.g. National Institute for Health and Care Excellence, All Wales Medicines Strategy Group or Scottish Medicines Consortium).

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. Supporting information

Systemic corticosteroids

- CTAG have made two recommendations with relation to the use of systemic corticosteroids to treat COVID-19 disease:
    - To use systemic (intravenous or oral) corticosteroid therapy in patients with WHO-defined 'severe'[a] or 'critical'[b] COVID-19, or in those patients who otherwise has a new oxygen requirement;
    - **Not to use** corticosteroid therapy in patients with WHO-defined non-severe COVID-19 (i.e. the absence of any signs of severe or critical COVID-19).
- Results from the REACT meta-analysis (which includes results from the RECOVERY and REMAP-CAP trials) demonstrated that administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality (full results in Appendix 1).[7]
- The CMO[8] advises clinicians that the WHO guidance is intended to apply globally; in the UK setting, it is likely to apply primarily to hospitalised patients with COVID-19 receiving oxygen, but there may be occasions where patients meet the WHO criteria of severe[a] or critical[b] but are not hospitalised (in which case the WHO guidance for treatment would apply).
- Co-administration of corticosteroids with remdesivir has not been fully studied but based on metabolism and clearance a clinically significant interaction is unlikely.
- CTAG are of the opinion that the administration of corticosteroids should not prejudice enrolment into interventional clinical trials.
- Further information can be found in the NICE prescribing briefing on corticosteroids.

3.1. There are no immunomodulatory medicines licensed to treat COVID-19 associated hyperinflammation.

3.2. Several immunomodulatory medicines are being investigated for the management of COVID-19 associated hyperinflammation; the evidence-base for these medicines is summarised in Appendix 1.

3.3. Hospitals managing COVID-19 cases should make every effort to enrol COVID-19 patients in national priority clinical trials[9–11] – refer to Section 4.

3.4. The following nationally prioritised trials for investigative immunomodulatory medicines are open to recruitment (Figure 3) and some allow concurrent dexamethasone (Table 1 for full details):
    - RECOVERY (in hospital trial; UK study open to all Trusts) added a second randomisation for patients with progressive disease and evidence of hyperinflammation
    - REMAP-CAP (critical care trial; international with UK sites) added immunomodulatory and anti-viral domains for COVID-19

[a] severe COVID-19 is defined as any of the following: (1) oxygen saturation < 90% on room air, (2) respiratory rate > 30 breaths per minute in adults and children >5 years; ≥ 40 in children 1–5 years; ≥ 50 in children 2–11 months; and ≥ 60 in children <2 months. (3) signs of severe respiratory distress (i.e. accessory muscle use, inability to complete full sentences; and in children, very severe chest wall indrawing, grunting, central cyanosis, or any other general danger signs).

[b] Critical covid-19 is defined as ARDS, sepsis, septic shock or other conditions normally requiring provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy

- ACCORD-2 (in hospital trial; UK multicentre study)
- CANCOVID (International study with UK sites)
- RUXCOVID (International study with UK sites)
- CATALYST (UK study, multicentre)
- TACTIC-R (UK study, multicentre)
- REALIST (UK study, multicentre)
- ILIAD-7-UK (UK study, single centre)
- STOP-COVID19 (UK study, multicentre)
- OSCAR (International study with UK sites)

3.5. The off-label or 'non-trial' use of immunomodulatory medicines should be avoided because:
- Medicines currently available within the NHS supply chain are needed for the patients already prescribed within licensed indications.[12]
- Medicines supplies are limited therefore their use outside the context of a clinical trial may compromise the feasibility of required trials.

3.6. 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.

3.7. Suspected side effects to medicines used in coronavirus treatment should be reported via the Yellow Card COVID-19 reporting site: https://coronavirus-yellowcard.mhra.gov.uk/

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 medicines for SARS-CoV-2 is available at https://www.ctag-support.org.uk/antivirals.

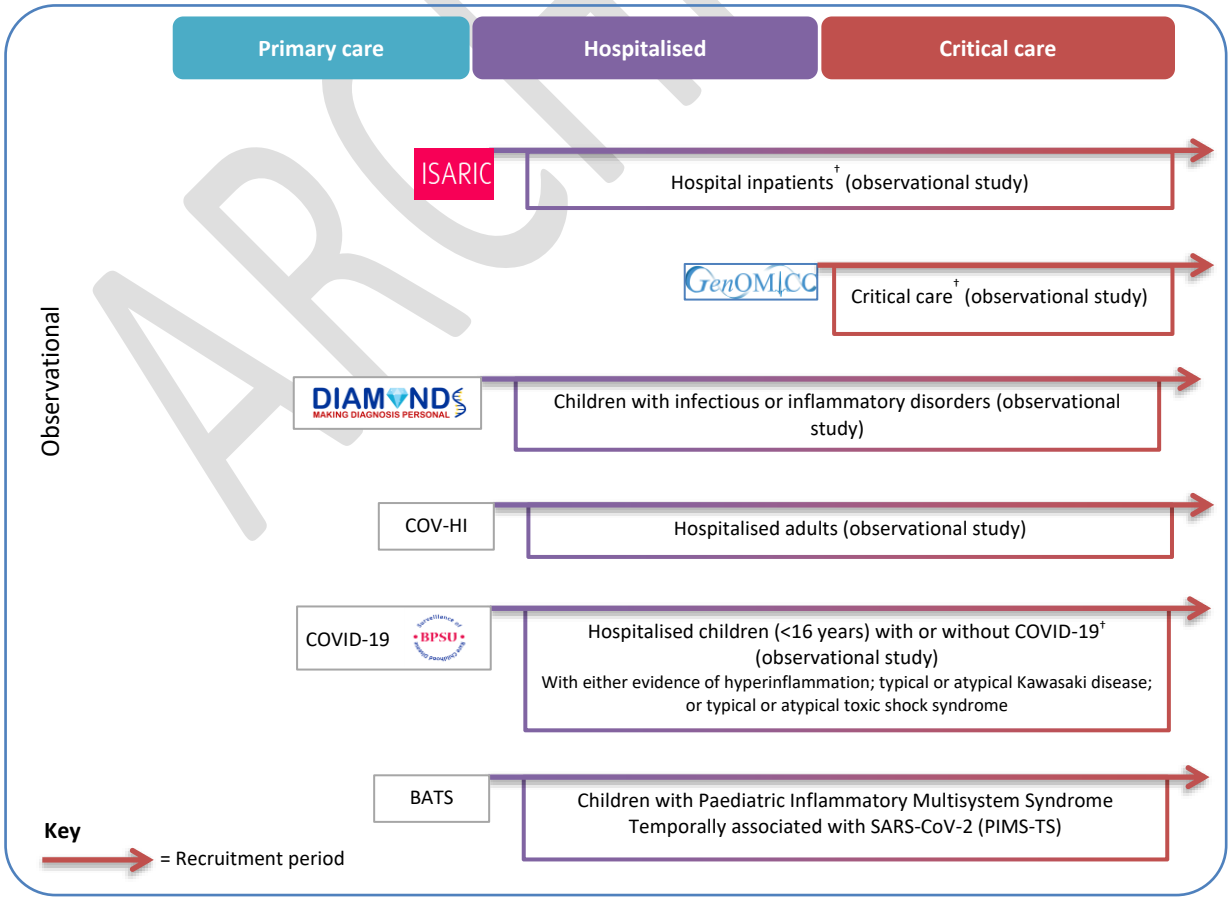

Figure 2: Recruiting UK Observational Studies as of 09 June 2020. † Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/.

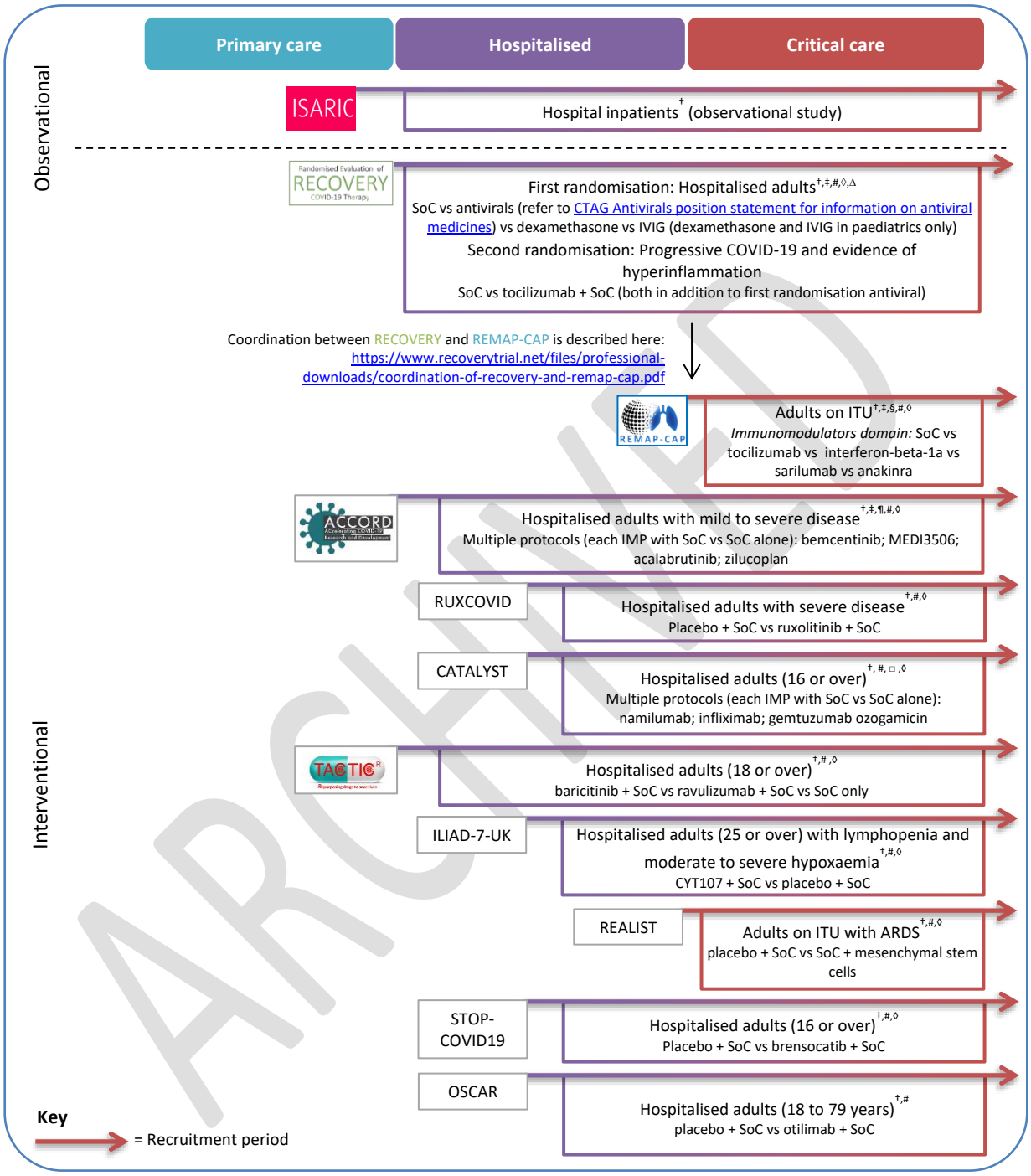

Figure 3: Immunomodulatory components of recruiting UK Clinical Studies as of 13 September 2020. SoC; standard of care. † Nationally prioritised research study for COVID-19 https://www.nihr.ac.uk/covid-studies/. ‡ These studies also include domains which are outside the scope of this document (e.g. antivirals, ventilation strategies, anticoagulation). § Tocilizumab is active at some sites; sarilumab, interferon-beta-1a and anakinra will be available to sites shortly. ¶ Not all treatment arms are currently active. # Concurrent use of dexamethasone permitted (except with interferon arm of REMAP-CAP, and caution with corticosteroid domain); studies without this annotation have not confirmed whether dexamethasone before or during the study is permitted □ Infliximab and namilumab arms have been prioritised and are recruiting; gemtuzumab ozogamicin is not currently recruiting but may be open to recruitment in the future. ◊ Concurrent use of remdesivir permitted (except REMAP-CAP if >36hrs of treatment has been received). Studies without this annotation have not confirmed whether the use of remdesivir before or during the study is permitted. Δ The IVIG arm may not be open at all trial sites.

4. UK clinical studies investigating immunomodulatory medicines

4.1. The NIHR is working with the Department of Health and Social Care to coordinate the national research agenda.[13]

4.2. Organisations should prioritise support for studies which have been nationally prioritised.[13] Non-prioritised research should continue, subject to it not having a negative impact on the system's ability to recruit participants and provide the resources needed to support priority clinical studies.[10]

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

4.4. 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 3: Closed to recruitment

4.5. For trials investigating antiviral medicines, please refer to https://www.ctag-support.org.uk/antivirals

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

Status	Trial		Population	Specific to hyperinflammation?	Intervention arms
Recruiting	Interventional	RECOVERY†,‡,#,◊,Δ (UK study open to all Trusts) (ISRCTN50189673)	First randomisation: Hospital inpatients; adults and paediatrics (any age) 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) vs dexamethasone vs IVIG (dexamethasone and IVIG in paediatrics only) 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 domain for COVID-19: – SoC – Tocilizumab – Interferon-beta-1a – Anakinra – Sarilumab
		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.
		REALIST†,#,◊ (UK study, multicentre) (NCT03042143)	Critical care; mechanically ventilated patients with Acute Respiratory Distress Syndrome with confirmed COVID-19	No	– SoC + Human umbilical cord derived CD362 enriched mesenchymal stem cells – SoC + placebo (Plasma-Lyte 148)

Status	Trial		Population	Specific to hyperinflammation?	Intervention arms
Recruiting	Interventional	ACCORD-2[†,‡,¶,◊] (UK study, multicentre) (Eudract 2020-001736-95)	Adult inpatients with confirmed SARS-CoV-2 infection; mild disease (with or without oxygen therapy) or severe disease (with non-invasive ventilation or high flow oxygen). Note: inclusion/exclusion criteria may vary between subprotocols	No	Multiple subprotocols: – Bemcentinib + SoC vs SoC – MEDI3506 + SoC vs SoC – Acalabrutinib + SoC vs SoC – Zilucoplan + SoC vs SoC
		CATALYST[†,#,□,◊] (UK study, multicentre) (Eudract 2020-001684-89)	Hospital inpatients; adults (16 or older) with confirmed COVID-19 (SaO2 of ≤ 94% on room air or PaO2:FiO2 ≤ 300 mmHg)	No	– Namilumab + SoC vs SoC alone – Infliximab + SoC vs SoC alone – Gemtuzumab ozogamicin + SoC vs SoC alone
		TACTIC-R[†,#,◊] (UK study, multicentre) (NCT04390464)	Adult patients (18 or over) with confirmed or suspected COVID-19	No	– Baricitinib + SoC – Ravulizumab + SoC – SoC only Note: Patients to be maintained on VTE prophylaxis or current maintenance therapy as per local guidelines.
		ILIAD-7-UK[†,#,◊] (UK study, single centre) (NCT04379076)	Adult inpatients (25 or over) with confirmed COVID-19, moderate to severe hypoxaemia and lymphopenia	No	– CYT107 + SoC – Placebo + SoC
		STOP-COVID19[†,#,◊] (UK study, multicentre) ISRCTN30564012	Adult inpatients (16 or over) with confirmed COVID-19 with either radiographic infiltrates, evidence of rales/crackles, SpO_2 ≤94% on room air, requiring supplemental oxygen or lymphocyte count <1x10^9 cells/L	No	– Brensocatib + SoC – Placebo + SoC
		OSCAR[†] (International study with UK sites) NCT04376684	Hospital inpatients; adults aged 18-79 with confirmed COVID-19, new onset hypoxia requiring significant oxygen support or early invasive mechanical ventilation (≤48 hours of intubation) and increased biological markers or systemic inflammation	No	– Otilimab + SoC – Placebo + SoC

Status	Trial		Population	Specific to hyperinflammation?	Intervention arms
Recruiting	Observational	ISARIC-CCP† (International study) (NCT04262921)	Hospital inpatients (children and adults); confirmed COVID-19	N/A	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	N/A	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	N/A	N/A – study designed to understand which patients are more likely to develop hyperinflammation associated with COVID-19.
		Neonatal complications of coronavirus disease (COVID-19)† (UK study)	Children <16 years with or without COVID-19, with either evidence of hyperinflammation; typical or atypical Kawasaki disease; or typical or atypical Toxic Shock Syndrome	N/A	N/A – study designed to understand the incidence and prevalence of new hyperinflammatory syndrome in relation to COVID, and compared to Kawasaki disease or Toxic Shock Syndrome.
		DIAMONDS† (International study)	Children and adults with infectious and inflammatory disorders including COVID and COVID-related inflammatory syndromes	N/A	N/A – study designed to identify gene signatures and develop molecular tests that distinguish different infections and inflammatory conditions
		BATS (Best Available Treatment Study) (International study) ISRCTN69546370	Children with Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS)	Yes	N/A – Non-consented retrospective data collection at sites treating children with PIMS-TS using Redcap database. Aims to identify best treatments through comparison of the response to different anti-inflammatory drugs used in different hospital settings

† 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. ¶ Not all treatment arms are currently active ◊ Concurrent use of remdesivir permitted (except REMAP-CAP if >36hrs of treatment has been received). Studies without this annotation have not confirmed whether the use of remdesivir before or during the study is permitted. # Concurrent use of dexamethasone permitted (except with interferon arm of REMAP-CAP, and caution with corticosteroid domain); studies without this annotation have not confirmed whether dexamethasone before or during the study is permitted □Infliximab and namilumab arms have been prioritised and are recruiting; gemtuzumab ozogamicin is not currently recruiting but may be open to recruitment in the future. Δ The IVIG arm may not be open at all trial sites.

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

Table 3: Closed to recruitment in the UK – Immunomodulatory interventional clinical trials

Status	Trial	Population	Interventions
Closed to recruitment	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)	– SoC – Tocilizumab + SoC
	ACTT-II† (International Phase III study) (NCT04401579)	Hospital inpatients; adults (18 or older) with confirmed COVID-19 and one of the following: radiographic infiltrates by imaging; SpO2 ≤94% on room air; requirement for supplemental oxygen; or mechanical ventilation or ECMO	– Remdesivir + Baricitinib – Remdesivir + Placebo
	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	– 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.
	REMAP-CAP† (International study with UK sites) (NCT02735707)	Critical care; adults with suspected or confirmed COVID-19	Corticosteroid domain for COVID-19: – SoC – Hydrocortisone for 7 days – Hydrocortisone whilst in septic shock

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

5. Corticosteroids for the treatment of COVID-19

Corticosteroids – Clinical guidance[6,8,14,15]				
Indication	**Dose and duration**	**Interactions**	**Additional information**	**Pregnancy/Breastfeeding**
• Patients with severe or critical COVID-19 – in line with WHO guidance, this includes: ○ acute respiratory distress syndrome (ARDS) ○ sepsis or septic shock ○ other conditions that would normally need life-sustaining therapies such as ventilation or vasopressor therapy ○ signs of severe respiratory distress ○ oxygen saturation 30 breaths per minute in adults and children over 5 years) ○ increased respiratory rate (>30 breaths per minute in adults and children >5 years; ≥ 40 in children 1–5 years; ≥ 50 in children 2–11 months; and ≥ 60 in children <2 months) • Patients with a new oxygen requirement	**Adult dosing:** *For dexamethasone 2mg tablets:* Three tablets (6mg) once daily for 7-10 days *Swallowing difficulties/enteral feeding: tablets can be crushed and mixed with water* *For dexamethasone 2mg/5mL oral solution:* 15mL (6mg) once daily for 7-10 days *For dexamethasone 3.3mg/mL IV ampoules* (only if tablets/liquid are inappropriate or unavailable): 1.8mL (5.94mg) once a day for 7-10 days *For IV hydrocortisone:* 50mg given three times daily for 7-10 days; up to 28 days can be considered for patients with septic shock **Use in children, pregnant or breastfeeding women:** Please refer to the SPC for dexamethasone and hydrocortisone.	• Co-administration of corticosteroids with remdesivir has not been studied. • A clinically significant interaction between dexamethasone or hydrocortisone with remdesivir is unlikely.	• Consider gastric ulcer protection with PPI if at risk of gastrointestinal bleeding • Consider other cautions and contraindications to steroid therapy • Corticosteroids should **not** normally be used in people with COVID-19 that is not 'severe' or 'critical' because there is the possibility of harm. • Hospitals should not order more than two weeks expected demand of corticosteroids at a time. • Trials only recruited adults; prescribers should consider the reduced risk of death observed with adults balanced with the risk associated with treatment	• If a person is pregnant or breastfeeding, the benefits of corticosteroids are thought to outweigh the risks. There is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities

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).

Subgroup membership (listed in alphabetical order, first by organisation, then surname):

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** Subgroup co-convenors*

The immunomodulatory subgroup will refer specific agenda items to HASC for consideration. HASC has approximately 150 members with multispecialty representation from across the UK; for more information regarding HASC, please contact Rachel.Tattersall@nhs.net. For the purposes of clarity, HASC is not a subgroup of CTAG although HASC co-Chairs do form part of the immunomodulators subgroup.

Document control

Date	Version	Amendments
22 April 2020	1.0	New document
07 May 2020	1.1	Updated evidence summaries in Appendix 1.
01 June 2020	2.0	Updated tables of trials and evidence summaries to include new proposed investigational products
16 June 2020	2.1	Updated Table 1, Table 2 and Appendix 1 in line with new available trials, investigational medicines and confirmation where access to remdesivir EAMS is permitted prior to or during trial. Added mechanism of action to Table A1.
30 June 2020	3.0	Included information on dexamethasone following the CMOs letter reporting on preliminary positive results from the RECOVERY trial
10 August 2020	4.0	Updated information for open trials and new emerging evidence Evidence tables method updated; tables split into those where benefit may exceed risk and where there is inadequate data to recommend use
15 October 2020	5.0	Updated to include new evidence and guidance on corticosteroids from WHO and letter from the CMO office. Additional advice from CTAG to consider dexamethasone in patients with a new oxygen requirement)

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

From V4.0, we updated our methodology to only summarise data for anti-inflammatory medicines with UK marketing authorisations being investigated to treat COVID-19 via NIHR nationally prioritised studies; this focuses evidence-tables to medicines which have the potentially to be used off-label in the UK.

Study identification is via Cochrane 'living' systematic literature review and meta-analysis and is supplemented by relevant information (including press-releases) identified through NICE Daily Medicines Awareness bulletins or other distribution methods.

The summaries are divided into two categories in the following tables based on current evidence:

- **Table A1**: Benefit may exceed risk
- **Table A2**: Inadequate data to recommend use

Healthcare professionals involved in the prescription and administration of an investigative agent should familiarise themselves with the medication safety profile before use.

Table A1: Evidence base for specific therapies for COVID-19 related hyperinflammation: Benefit may exceed risk

	Therapy	Data: Other forms of hyperinflammation	Data: COVID-19 induced hyperinflammation	Safety profile	UK feasibility
Corticosteroids	Cortico-steroids	Corticosteroids (such as dexamethasone, prednisolone, methylprednisolone or hydrocortisone) are immunosuppressive medicines that bind to the glucocorticoid receptor, which can bind and inactivate proinflammatory transcription factors, upregulate cytokine inhibitory proteins or reduce the half-life time and utility of cytokine mRNA.[16] Favourable modulation of the immune response is considered one of the possible mechanisms by which corticosteroids might be beneficial in the treatment of severe acute respiratory coronavirus infections, including COVID-19, SARS and MERS.[17] A review of previous clinical data for corticosteroid therapy found no clinical data to indicate net clinical benefit from corticosteroids in the treatment of respiratory infection due to respiratory syncytial virus, influenza, SARS-CoV or MERS-CoV.[18] Corticosteroids are a recognized therapeutic option in hyperinflammation.[5,19]	A meta-analysis of seven randomised clinical trials (n=1703) reviewed the association between administration of corticosteroids (n=678) compared with placebo or SoC alone (n=1025) and 28-day mortality in critically ill patients.[7] The primary outcome measure was all-cause mortality up to 30 days after randomisation. Participants were a median age of 60 years and 29% were women. The meta-analysis included patients from REMAP-CAP and the RECOVERY trial (though only the patients who received mechanical ventilation was included from RECOVERY). The RECOVERY trial contributed to 59.1% of patients in this meta-analysis. The number of patients across trials with PCR confirmed SARS-CoV-2 ranged from 78.7% to 100%. Risk of bias was evaluated as 'low' for six of the seven studies and as "some concerns" in one study due to the randomisation method. There were 222 deaths in the patients randomised to corticosteroids versus 425 deaths in the patients randomised to placebo/SoC (summary OR = 0.66 [95% CI 0.53 to 0.82]). There was little inconsistency between trial results (I^2 = 15.6%; p=0.31). The random-effects meta-analysis results were not significant (summary OR = 0.70 [95% 0.48 to 1.01]). The fixed-effects summary OR for the association with mortality compared with SoC/placebo was significant for dexamethasone (1282 patients, three trials; summary OR = 0.64 [95% CI 0.50 to 0.82]) but not for hydrocortisone (374 patients, three trials; summary OR = 0.69 [95% CI, 0.43 to 1.12]) or methylprednisolone (47 patients, one trial; summary OR = 0.91 [95% CI 0.29 to 2.87]). Low-dose corticosteroid versus SoC/placebo was significant but larger doses of corticosteroid versus SoC/placebo was not (which authors suggest is imprecisely estimated). Other subgroup analyses favoured corticosteroids (except for patients taking vasoactive agents at randomisation). One additional trial using methylprednisolone was later identified; by including only mechanically ventilated patients from the study, there was little impact to the fixed-effects OR for corticosteroids versus placebo/SoC. Limitations include two studies that did not contribute to the data analysis, one study showing some concern in bias, missing outcome data from trials, variation in the time to endpoint amongst studies, the lack of data in children and a majority of the data coming from one trial.	A secondary outcome from the REACT meta-analysis[7] was investigator-defined serious adverse events. The RECOVERY trial did not record serious adverse events. Among the other trials, 64 events occurred in 354 patients randomised to corticosteroid versus 80 events in 342 patients randomised to SoC or placebo. Risk of bias was "low" in two of six studies for serious adverse events, whilst the other four had "some concerns" based on subjectively implying that classification of serious adverse events could differ between groups. Please see links below for more information on safety of the medication within the marketing authorisation. Dexamethasone: SPC (tablet, oral solution or IV) or BNF Hydrocortisone: SPC (tablet or IV) or BNF Prednisolone tablet: SPC or BNF Methylprednisolone IV: SPC or BNF	Previously an interventional treatment arm in the RECOVERY and REMAP-CAP trials

Table A2: Evidence base for specific therapies for COVID-19 related hyperinflammation: Inadequate data to recommend use

	Therapy	Data: Other forms of hyperinflammation	Data: COVID-19 induced hyperinflammation	Safety profile	UK feasibility
Interleukin-1 inhibitor	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 in the UK to treat Still's disease (including systemic juvenile idiopathic arthritis and Adult-Onset Still's disease), which is recognized in progressing to hyperinflammation.[19,20] 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'[21] or 'disseminated intravascular coagulation and hepatobiliary dysfunction'[22] (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[23–27] find a high proportion of patients with sHLH/macrophage activation syndrome (MAS) treated with anakinra survive. These reports were limited by the lack of a control arm, and small number of patients. In a recent NICE evidence summary, it is advised that policy decisions on anakinra for COVID-19 associated sHLH will need to consider data extrapolated from studies assessing anakinra for other hyperinflammatory states.	The highest level of evidence is a NICE evidence summary (correct to 13 May 2020), which was performed a review to determine the efficacy, safety, cost-effectiveness and potential benefit to particular subgroups from the administration of anakinra for COVID-19 associated sHLH in patients of all ages.[28] No relevant published papers were identified. Two unpublished, non-peer reviewed papers were identified (one was a systematic review in preprint that did not identify any published literature on anakinra; the other was a case-series in seven intensive care patients and one non-intensive care patient in preprint, in which laboratory outcomes and respiratory function improved but three patients died)[29,30].	The NICE evidence summary recognizes that newer studies consider intravenous anakinra for related hyperinflammatory states in patients with COVID-19 and ARDS, and warns that this is off-label use which raises safety concerns. Caution is also advised when using such immunomodulatory therapies in critically ill people with suspected infection due to the risk of complications. However, it is proposed that anakinra may be an option if immunomodulation is considered necessary because it has a relatively short half-life and can be discontinued quickly if an adverse effect or concern for worsening infection arises. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	An active interventional arm in the REMAP-CAP trial.

	Therapy	Data: Other forms of hyperinflammation	Data: COVID-19 induced hyperinflammation	Safety profile	UK feasibility
Interleukin-1 inhibitor	Canakinumab	Canakinumab binds with interleukin-1 beta to prevent its inflammatory activity. It is licensed in the UK 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 are yet reported on the Cochrane database of COVID-19 trials.	No safety data has been reported on the Cochrane database of COVID-19 trials. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	An interventional treatment arm in CANCOVID

	Therapy	Data: Other forms of hyperinflammation	Data: COVID-19 induced hyperinflammation	Safety profile	UK feasibility
Interleukin-6 inhibitor	Tocilizumab	Tocilizumab binds to both soluble and membrane bound interleukin-6 receptors, and is licensed in the UK following demonstration of efficacy in treating CRS associated with the CAR-T therapies such as tisagenlecleucel and axicabtagene ciloleucel.[31] 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.	The highest level of evidence is only available as a press release currently; a randomised, double-blind, placebo-controlled trial in patients with COVID-19 associated pneumonia (the COVACTA trial)[32] reports that tocilizumab did not reach its primary endpoint (improvement in clinical status) versus placebo (OR = 0.36 [95% CI 0.81 to 1.76]). It also did not reach the key secondary endpoint (reduction in patient mortality) versus placebo (mortality rate 19.7% vs 19.4%; absolute difference 0.3% [95% CI -7.6% to 8.2%]). A publication in a peer-reviewed journal is awaited. The Cochrane database of COVID-19 trials found four non-randomised studies with favourable outcomes. Somers et al[33] found a significant reduction in mortality rate but also a significant association for tocilizumab with 'superinfections'. Ip[34] et al performed an exploratory analysis that demonstrated a trend towards an improvement in survival with tocilizumab. Rossi[35] et al performed a comparison of 84 propensity-matched pairs of patients and found there were fewer incidences of the primary outcome (a composite of death and ventilation) associated with tocilizumab use. Martinez-Sans[36] et al performed a cohort study in which a crude analysis found tocilizumab to be associated with an increased risk of death or a composite of ICU admission & death; however, in an adjusted analysis in patients with high CRP values, tocilizumab was associated with significantly lower rates of death or composite of ICU admission & death.	From the COVACTA press release, post-treatment rates of infection were 38.3% for tocilizumab and 40.6% in the placebo arms respectively (21.0% versus 25.9% respectively for serious infections).[32] A publication in a peer-reviewed journal is awaited. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	An interventional arm of the REMAP-CAP and RECOVERY trials. Previously an interventional treatment arm in the COVACTA trial.

	Therapy	Data: Other forms of hyperinflammation	Data: COVID-19 induced hyperinflammation	Safety profile	UK feasibility
Interleukin-6 inhibitor	Sarilumab	Sarilumab binds to both soluble and membrane bound interleukin-6 receptors, preventing IL-6 mediated signalling. It is licensed in the UK for the treatment of moderate to severe rheumatoid arthritis.[37] 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)[38] 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 further press release reports that sarilumab 400mg did not meet its primary and key secondary endpoints when given to 194 critically ill COVID-19 patients requiring mechanical ventilation.[39] A publication in a peer-reviewed journal is awaited. Studies using alternative dosing regimens outside the US are ongoing.	No safety data has been reported in the COVID-19 population. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	Proposal to add as an interventional arm to the RECOVERY trial. An interventional treatment arm in the REMAP-CAP trial.
	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.[40] 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.	The Cochrane database of COVID-19 trials has one observational study for siltuximab, which has a favourable outcome.[41] The study is a case series in 21 patients in Italy, which reported 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 study 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 case series, one suffered a cerebrovascular event. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	Not available under a clinical trial in the UK currently

	Therapy	Data: Other forms of hyperinflammation	Data: COVID-19 induced hyperinflammation	Safety profile	UK feasibility
Janus Kinase Inhibitor	Ruxolitinib	Ruxolitinib is a selective Janus-associated kinase (JAK) 1 and 2 inhibitor responsible for cytokine signalling. Ruxolitinib is licensed in the UK to treat myelofibrosis and thrombocythaemia. A case report in which a patient was given ruxolitinib for sHLH refractory to standard of care therapy[42] (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. Six adverse events were reported and classified as a possible or probable consequence of ruxolitinib. One was a serious adverse event (febrile neutropenia) and one grade two adverse event of pain in extremity caused discontinuation. This study had a long follow-up period but is limited by the open-label single arm design and only five participants.[43] 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.[44]	The highest level of evidence is a prospective, multicentre, single-blind, randomized controlled phase II trial involving adult patients with severe COVID-19 conducted in China.[45] Forty-three patients were randomly assigned (1:1) to receive ruxolitinib 5 mg twice daily plus SoC (n=22) or placebo plus SoC (n=21). Two patients were excluded from the ruxolitinib group (one ineligible and one withdrew consent). The primary efficacy endpoint was time to clinical improvement by two points on a seven-category ordinal scale or discharge from the hospital and improvement on CT scan at day 14. Treatment with ruxolitinib plus SoC was not associated with significantly accelerated clinical improvement, although ruxolitinib recipients had numerically faster clinical improvement. 18 (90%) patients from the ruxolitinib group showed CT improvement at day 14 compared with 13 (61.9%) patients from the placebo group (P = 0.0495). Three patients died in the placebo group versus none in the ruxolitinib group. Levels of seven different cytokines significantly decreased in the ruxolitinib group compared to the control group. The study is limited by the exclusion of several patient groups at recruitment (including those who may have poorer outcomes, such as those mechanically ventilated or over the age of 75), not meeting the target sample size of 70 due to decelerating enrolment, the small sample size and being single-blinded.	In the randomized controlled trial, 16 patients in the ruxolitinib group reported an adverse event versus 15 in the placebo group.[45] One patient in the ruxolitinib group developed grade 3 lymphopenia after four days, which improved after a further two days without interrupting ruxolitinib treatment. Grade 3 hypertension developed in one patient taking ruxolitinib; this was judged to be due to the study medication, though transient and reversible. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	An interventional treatment arm in RUXCOVID

	Therapy	Data: Other forms of hyperinflammation	Data: COVID-19 induced hyperinflammation	Safety profile	UK feasibility
Janus Kinas e Inhibitor	Baricitinib	Baricitinib is a JAK1 and JAK2 reversible inhibitor responsible for cytokine signaling. It is licensed in the UK to treat moderate to severe active rheumatoid arthritis. A recent publication suggests baricitinib could also prevent SARS-CoV-2 endocytosis through other mechanisms (inhibition of AP-2 associated protein kinase 1 (AAK1) and binding to cyclin-g associated kinase (GAK), both of which regulate endocytosis through lung AT2 alveolar epithelial cells).[46] A literature search could not identify any studies using baricitinib to treat other hyperinflammatory states.	The Cochrane database of COVID-19 trials has one observational study for baricitinib that has a favourable outcome.[47] The single-centre observational study used a combination of hydroxychloroquine and baricitinib. Following initiation of baricitinib, 13 out of 15 patients had a significant reduction in body temperature and CRP levels over the course of treatment. There was 80% survival at the end of the study period; three patients died. The study is limited by the low patient number, lack of a control arm, lack of randomisation and concomitant use of hydroxychloroquine.	From the observational study, thrombotic events occurred in three patients. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	An interventional treatment in TACTIC-R. Proposed as an interventional treatment arm in ACTT-II.
Bruton tyrosine kinase inhibitor	Acalabrutinib	Acalabrutinib is a Bruton tyrosine kinase (BTK) inhibitor licensed by the FDA licensed to treat chronic lymphocytic leukaemia and mantle cell lymphoma (currently unlicensed in the UK). Acalabrutinib binds in the active site of BTK, which prevents downstream activation of B-cell proliferation and cytokine receptor pathways. The manufacturer suggests dysregulated BTK-dependent macrophage signaling may be central to the production of multiple inflammatory cytokines and chemokines, leading to an exaggerated inflammatory response.[48] A literature search could not identify any studies using acalabrutinib to treat other hyperinflammatory states.	No results are yet reported on the Cochrane database of COVID-19 trials.	No safety data has been reported on the Cochrane database of COVID-19 trials. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	An interventional treatment arm in ACCORD-2.

	Therapy	Data: Other forms of hyperinflammation	Data: COVID-19 induced hyperinflammation	Safety profile	UK feasibility
CD-33 mAb and calichaemicin	Gemtuzumab ozogamicin	Gemtuzumab ozogamicin is a recombinant antibody conjugated with a calicheamicin cytotoxic antibiotic licensed in the UK as part of a protocol to treat CD-33 positive acute myeloid leukaemia. It binds to the CD-33 antigen expressed by haematopoietic cells and is internalized, followed by release of the calicheamicin derivative binds to the DNA and induces cell death. A study in mice models with hallmarks of HLH/MAS found ablation of myeloid cells (and not lymphoid cells) reversed the disease process; gemtuzumab ozogamicin was effective in restoring red cell count, improving appearance, splenomegaly and bone marrow cellularity. Targeting CD33 was proposed as a potential therapeutic approach in cases refractory to current therapies.[49] A literature search could not identify any studies using gemtuzumab ozogamicin to treat other hyperinflammatory states.	No results are yet reported on the Cochrane database of COVID-19 trials.	No safety data has been reported on the Cochrane database of COVID-19 trials. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	An interventional treatment arm in CATALYST.
Terminal complement inhibitor	Ravulizumab	Ravulizumab is a terminal complement inhibitor specific to protein C5 with high affinity, preventing the formation of C5a, C5b and C5b9. It is licensed in the UK for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria. A study in mice infected with SARS-CoV identified the complement system to be an important mediator and suggests that complement activation regulates a systemic inflammatory response to SARS-CoV.[50] A literature search could not identify any studies using ravulizumab to treat other hyperinflammatory states.	No results are yet reported on the Cochrane database of COVID-19 trials.	No safety data has been reported on the Cochrane database of COVID-19 trials. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	An interventional treatment in TACTIC-R.

	Therapy	Data: Other forms of hyperinflammation	Data: COVID-19 induced hyperinflammation	Safety profile	UK feasibility
Tumour necrosis factor blocker	Infliximab	Infliximab is a tumor necrosis factor (TNF) blocker licensed in the UK for several inflammatory conditions such as rheumatoid arthritis and Crohn's disease. A study identified TNF as one of the key cytokines involved in the pathogenesis of macrophage activation syndrome (MAS) associated with Kawasaki Disease.[51] There are several case reports on the efficacy of infliximab being used to treat several forms of hyperinflammation, such as MAS and HLH, sometimes in combination with other immunomodulators.[52–55] There are also cases reports detailing the risk of infliximab causing a secondary infection which can lead to hyperinflammation and of infliximab not providing therapeutic benefit.[56–58]	No results are yet reported on the Cochrane database of COVID-19 trials.	No safety data has been reported on the Cochrane database of COVID-19 trials. Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	An interventional treatment arm in CATALYST
Immunoglobulin (for PIMS-TS)	Intravenous Immuno-globulin (IVIG)	IVIG is an established treatment for immunomodulation in children and adults (such as Kawasaki disease and Guillain-Barré syndrome). Randomised controlled trials and meta-analyses have demonstrated that early recognition and treatment of Kawasaki disease with IVIG (and aspirin) reduces the occurrence of coronary artery aneurysms.[59]	No results are yet reported on the Cochrane database of COVID-19 trials (specifically for PIMS-TS).	No safety data has been reported on the Cochrane database of COVID-19 trials (specifically for PIMS-TS). Please see the SPC or BNF for more information on safety of the medication within the marketing authorisation.	An interventional arm of the RECOVERY 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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