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Therapeutic blockade of granulocyte macrophage colony-stimulating factor in COVID-19-associated hyperinflammation: challenges and opportunities

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The COVID-19 pandemic is a global public health crisis, with considerable mortality and morbidity exerting pressure on health-care resources, including critical care. An excessive host inflammatory response in a subgroup of patients with severe COVID-19 might contribute to the development of acute respiratory distress syndrome (ARDS) and multiorgan failure. Timely therapeutic intervention with immunomodulation in patients with hyperinflammation could prevent disease progression to ARDS and obviate the need for invasive ventilation. Granulocyte macrophage colony-stimulating factor (GM-CSF) is an immunoregulatory cytokine with a pivotal role in initiation and perpetuation of inflammatory diseases. GM-CSF could link T-cell-driven acute pulmonary inflammation with an autocrine, self-amplifying cytokine loop leading to monocyte and macrophage activation. This axis has been targeted in cytokine storm syndromes and chronic inflammatory disorders. Here, we consider the scientific rationale for therapeutic targeting of GM-CSF in COVID-19-associated hyperinflammation. Since GM-CSF also has a key role in homoeostasis and host defence, we discuss potential risks associated with inhibition of GM-CSF in the context of viral infection and the challenges of doing clinical trials in this setting, highlighting in particular the need for a patient risk-stratification algorithm.

Introduction

As of June 10, 2020, more than 7·1 million confirmed cases of COVID-19 have been reported worldwide, and 408 025 people have died with the disease.[1] Acute respiratory distress syndrome (ARDS) and multiorgan failure are major causes of mortality in patients with COVID-19.[2]

There are felt to be two distinct but overlapping phases for therapeutic targeting of patients with COVID-19: an initial viral response followed by a host hyperinflammatory response.[3] We previously recommended screening for virally driven hyperinflammation in patients with severe COVID-19 and proposed that immunomodulation might reduce the high mortality in this group.[4] Therapeutic targets might include pro-inflammatory cytokines that are expected to be increased in hyperinflammatory disorders, such as interleukin (IL)-6, IL-1, or granulocyte macrophage colony-stimulating factor (GM-CSF).

Clinical trials of existing approved immunomodulatory agents, including inhibitors of the IL-6 pathway (eg, with tocilizumab) and IL-1 pathway (eg, with anakinra), are ongoing or about to start in patients with COVID-19. Moreover, the US Food and Drug Administration has approved emergency compassionate use of an anti-GM-CSF monoclonal antibody for patients with COVID-19,[5] despite no clinical trial evidence for the therapeutic approach in this setting. As of June, 2020, six companies were planning or seeking regulatory approval for clinical trials in COVID-19 using agents that either target GM-CSF or its receptor (table).

Here, we present accumulating evidence to support the scientific rationale for therapeutic targeting of GM-CSF in patients with hyperinflammation, ARDS, and hence in COVID-19-associated hyperinflammation. We also discuss potential risks associated with targeting GM-CSF in the context of viral infection and challenges of conducting clinical trials in this disease setting, and we provide details of planned clinical trials in COVID-19 using agents which either target GM-CSF or its receptor.

Key messages

- Immunomodulation during a window of opportunity in a subgroup of patients with hyperinflammation might reduce progression to acute respiratory distress syndrome (ARDS), obviate the need for intubation, and reduce the high mortality in patients with COVID-19
- Granulocyte macrophage colony-stimulating factor (GM-CSF), which signals via the JAK-STAT pathway and induces the production of interleukin-6 and other proinflammatory cytokines, could serve as a link between T-cell-driven acute pulmonary inflammation and an autocrine, self-amplifying cytokine loop leading to monocyte and macrophage activation
- GM-CSF has been pursued as a therapeutic target in trials of chronic inflammatory disease (eg, rheumatoid arthritis) and cytokine storm syndromes (eg, cytokine release syndrome associated with chimeric antigen receptor T-cell therapy)
- Emerging evidence supports targeting of GM-CSF in patients with hyperinflammation and ARDS, including those with COVID-19-associated hyperinflammation; blockade of GM-CSF or its receptor using monoclonal antibodies is currently being pursued in COVID-19 clinical trials
- Potential benefits of targeting GM-CSF in the context of virally driven hyperinflammation need to be carefully balanced against potential risks associated with blocking the role of GM-CSF in tissue homoeostasis and in antiviral immunity and host defence
- Cross-specialty collaboration and randomised controlled trials will be essential to establish the potential benefits and risks of targeting GM-CSF in subgroups of patients with COVID-19 and the optimum timing of treatment

Hyperinflammation and COVID-19

Hyperinflammation describes a spectrum of disorders. The terminology related to these disorders is

heterogeneous; however, they are referred to collectively as cytokine storm syndromes, which are treated with immunomodulatory agents to attenuate the excessive immunoinflammatory response. The hyperinflammatory condition haemophagocytic lymphohistiocytosis (HLH) is characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure, usually manifesting with cytopenia and abnormal liver function. When caused by genetic abnormalities, this disorder is referred to as primary or familial HLH. Secondary HLH is a hyperinflammatory syndrome triggered by infection, rheumatic disorders, and malignant disease (usually lymphoproliferative disorders). Cytokine storm syndromes can be termed macrophage activation syndrome (when associated with rheumatic disease), macrophage activation-like syndrome (in sepsis), and cytokine release syndrome (after chimeric antigen receptor [CAR] T-cell therapy).[3] A subset of patients with severe COVID-19 shows evidence of hyperinflammation and might, therefore, potentially benefit from immunomodulation.

ARDS is a heterogeneous clinical disorder characterised by refractory hypoxaemia, with mortality of 35–55% despite supportive standard of care, including low tidal volume ventilation. ARDS is defined by the development or worsening of hypoxaemia in the presence of bilateral pulmonary infiltrates and develops most commonly in response to community-acquired pneumonia. Cohort data from Wuhan, China,[12] show that ARDS occurs in approximately 30% of hospitalised patients with COVID-19 and is associated with high mortality. Clinical trials of pharmacological agents in ARDS have been met with limited treatment successes, but unbiased latent class analysis of clinical and biomarker characteristics from randomised trial data has identified two distinct ARDS subphenotypes—a hypoinflammatory endotype and a hyperinflammatory endotype—with distinct clinical characteristics, biomarker profiles, clinical outcomes, and treatment responses.[13] Therefore, it is increasingly recognised that a tailored therapeutic approach to individual ARDS patients will be needed to improve clinical outcomes.

The clinical presentation of severe COVID-19 seems to be unique and has been the subject of much discussion in the community. Emerging experience suggests that the hyperinflammatory response in COVID-19 does not fit the classic profile of secondary HLH or cytokine release syndrome. Although ferritin levels predict mortality in COVID-19,[2] ranges are lower than those reported in patients with secondary HLH, and the clinical syndrome is lung dominant, typically without substantial cytopenia. Of note, lymphopenia is almost universal in patients with severe COVID-19,[14] but the lymphocyte lineage is not classically affected in secondary HLH; in the context of COVID-19, therefore, lymphopenia might be the outcome of a viral driver. Whether patients with COVID-19 pneumonia present an atypical form of ARDS has also been debated,[15] but it is increasingly felt that ARDS associated with COVID-19 might not be dissimilar to the phenotype associated with other viral drivers. A management approach for COVID-19-associated ARDS has been proposed and is continuously evolving as clinical experience accumulates.[16]

The proinflammatory cytokine GM-CSF

GM-CSF was originally defined as a haematopoietic growth factor because of its ability to form colonies of granulocytes and macrophages in vitro by promoting proliferation and differentiation of bone marrow progenitor cells.[17] Later, GM-CSF was found to act on mature myeloid cells, such as macrophages and neutrophils, as a prosurvival or activating factor with a role in inflammation. Unlike other members of the colony-stimulating factor superfamily of pleiotropic growth factors (eg, macrophage colony-stimulating factor, granulocyte colony-stimulating factor [G-CSF]), GM-CSF does not seem to have a role in steady-state myelopoiesis.[17] Instead, GM-CSF plays a key role in tissue inflammation, with mounting evidence that it contributes to development of autoimmune and inflammatory diseases, including T-helper (Th)17-driven diseases such as ankylosing spondylitis.[18]

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	Study type (trial identification)	Study design, aims, and outcomes
Targeting GM-CSF receptor alpha		
Mavrilimumab (Kiniska, Lexington, MA, USA)	Pilot study (phase 2 trial planned; NCT04397497)	Single-centre pilot study in six patients with worsening pulmonary involvement and COVID-19 with biological markers of systemic hyperinflammation treated with one intravenous dose of mavrilimumab;[6] all six patients showed early resolution of fever and improvement in oxygenation within 1–3 days and three of six patients were discharged within 5 days[6]
Targeting GM-CSF		
Otilimab (GlaxoSmithKline)	Phase 2 (NCT04376684)	Multicentre, double-blind, randomised, placebo-controlled trial of single-dose otilimab in 800 patients (primary endpoint: proportion of participants alive and free of respiratory failure at day 28)
Lenzilumab (Humanigen, Burlingame, CA, USA)	Phase 3 (NCT04351152)	FDA approval for phase 3 study (primary endpoint: incidence of invasive mechanical ventilation or mortality)[7] and for emergency compassionate use[5]
Namilumab (Izana Bioscience, Oxford, UK)	Phase 2 planned (EudraCT 2020-001684-89; ISRCTN 40580903)	Two-centre compassionate-use study planned in Italy;[8] multicentre randomised trial of namilumab in COVID-19 planned in the UK platform study CATALYST[9]
Gimsilumab (Roivant, Basel, Switzerland)	Phase 2 (NCT04351243)	Adaptive, randomised, double-blind, placebo-controlled multicentre trial expected to enrol up to 270 patients with acute lung injury or ARDS (primary endpoint: mortality at day 43)[10]
TJ003234 (I-Mab, Shanghai, China)	Phase 1b/2 (NCT04341116)	FDA investigational new drug application clearance approved;[11] proposed multicentre, randomised, double-blind, placebo-controlled, three-arm study (primary endpoint: proportion of participants with deterioration in clinical status, on an eight-category ordinal scale)

ARDS=acute respiratory distress syndrome. FDA=US Food and Drug Administration. GM-CSF=granulocyte macrophage colony-stimulating factor.

Table: **Drugs targeting GM-CSF or its receptor in clinical studies in patients with COVID-19**

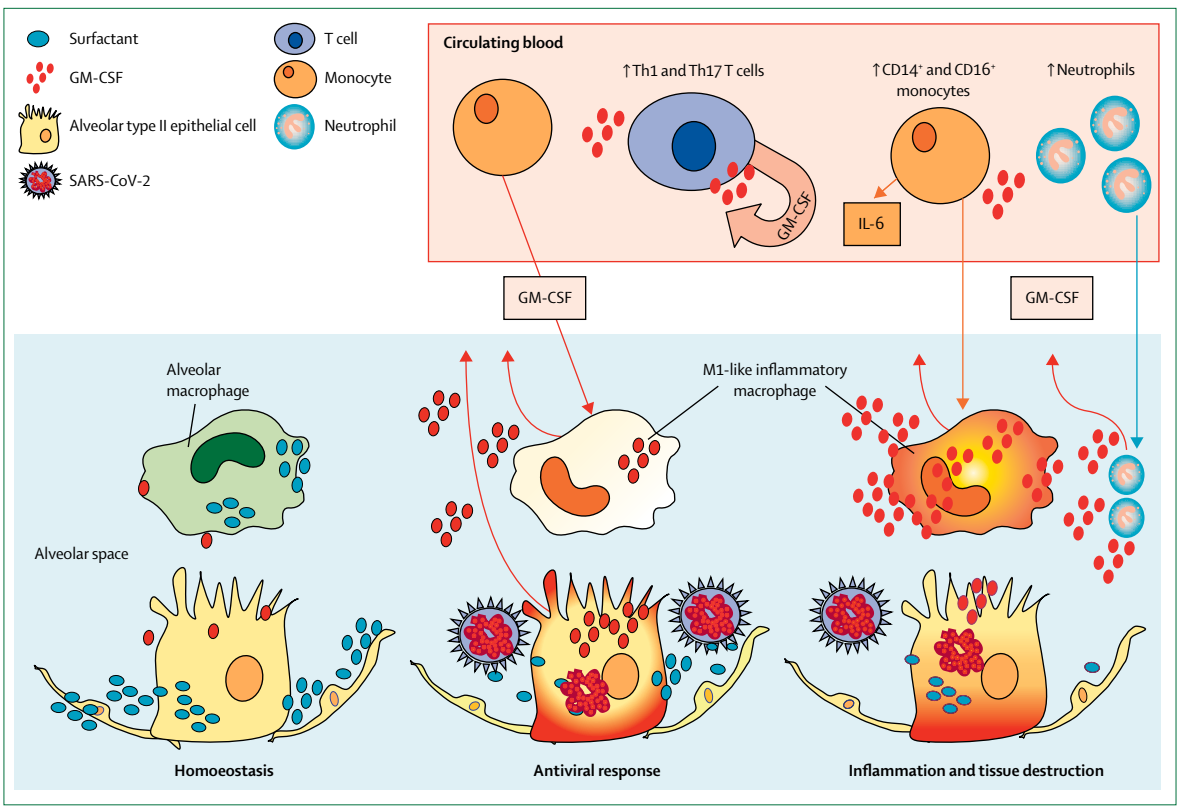

Figure 1: **Role of GM-CSF in homoeostasis, viral response, and inflammation**
GM-CSF has an important homoeostatic role in the maturation and function of alveolar macrophages, which clear and catabolise surfactant, and in host defence. In response to viral insults (eg, with SARS-CoV-2), alveolar type II epithelial cells secrete GM-CSF, improving the innate immune response of myeloid cells, particularly alveolar macrophages. In severe inflammatory states, GM-CSF production is upregulated by alveolar type II epithelial cells and monocyte-derived M1-like macrophages, thereby stimulating IL-6 production from $CD14^+$ and $CD16^+$ inflammatory monocytes, increasing Th1 and Th17 T cells and driving the recruitment and priming of neutrophils. The resulting autocrine, positive feedback loop of GM-CSF production further perpetuates the inflammatory milieu. GM-CSF=granulocyte macrophage colony-stimulating factor. IL=interleukin. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. Th=T helper.

GM-CSF is expressed locally in tissues such as the lung, gut, and skin, but it is virtually undetectable in the systemic circulation.[19] Multiple cellular sources of GM-CSF have been described. In the healthy lung, GM-CSF is secreted by alveolar type II epithelial cells (figure 1) and has a key role in maturation and function of alveolar macrophages, including surfactant catabolism. Congenital or acquired GM-CSF deficiency can lead to pulmonary alveolar proteinosis because of dysregulated surfactant clearance.[18] GM-CSF has an important host-defence function in maintenance of the integrity of the alveolar capillary barrier;[20,21] moreover, it has an immunostimulatory protective role in pathogenic clearance in the context of bacterial and virally triggered pneumonia or ARDS.[22–24]

Growing evidence suggests that GM-CSF is produced and acts locally at sites of tissue inflammation.[18] T cells seem to be the most prominent producers of GM-CSF in tissue inflammation, but epithelial cells, endothelial cells, fibroblasts, stromal cells, and haematopoietic cells can also all produce GM-CSF, commensurate with a role for this cytokine in integrating tissue-regulated inflammatory cell infiltration, even before T-cell migration. Local production of GM-CSF increases with inflammation,[18] and the level of this cytokine is increased in synovial fluid and serum from patients with rheumatoid arthritis, in cerebrospinal fluid from patients with multiple sclerosis,[18] and in bronchoalveolar lavage fluid from patients with ARDS.[25] GM-CSF is pivotal to proinflammatory cytokine networks,[17] including the cytokine cascade in HLH,[26] and it not only induces expression of tumour necrosis factor (TNF), IL-6, and IL-23, but also promotes differentiation of Th1 or Th17 cells and polarisation of macrophages to an M1-like phenotype.[18]

GM-CSF and neutrophils in hyperinflammation

Similar to GM-CSF, the cytokine G-CSF has a role in macrophage and antigen-presenting-cell activation and can increase neutrophil chemotaxis and migration, but response kinetics of GM-CSF and G-CSF can differ.[27] GM-CSF is considered to be more proinflammatory than is G-CSF.[27] G-CSF is postulated to interact with G-CSF receptors on monocytes, providing continuous stimulation with pharmacological rather than lower physiological concentrations of growth factor.[28] A feedback

mechanism might enhance the process with monokines, causing subsequent clonal expansion and activation of T lymphocytes. Activated T cells synthesise and secrete interferon (IFN)γ, GM-CSF, and TNF. These factors interact with the GM-CSF receptor and other receptors on the monocyte, providing additional and continuing stimulation of monocytes.

Emerging evidence suggests a role for GM-CSF in HLH, based on administration of recombinant G-CSF in patients with this disorder. In clinical practice, there are concerns that administration of G-CSF might worsen HLH; indeed, the observation that administration of recombinant G-CSF (eg, lenograstim) exacerbated synovitis supported the rationale to target the GM-CSF pathway in rheumatoid arthritis.[29] To the best of our knowledge, five cases have been reported of exacerbation of existing or de-novo provocation of HLH after administration of recombinant G-CSF or GM-CSF (appendix pp 1–2).[30–33] This experience warrants cautious use of recombinant G-CSF in critically ill patients with neutropenia and evidence of HLH.

Further evidence of a role for GM-CSF in HLH comes from murine models of both the primary and secondary disorder, in which GM-CSF has been shown to be elevated in untreated, active disease and significantly reduced with treatment aimed at JAK inhibition.[34] Moreover, a HLH-like disease was observed in lymphocytic choriomeningitis virus-infected IFNγ and Prf1 double knockout mice, with a cytokine milieu dominated by IL-6 and GM-CSF, similar to human HLH, challenging the dogma that IFNγ is mandatory for pathogenesis of HLH.[35] A humanised mouse model of post-allogeneic stem-cell transplant HLH showed increased GM-CSF levels, in parallel with other cytokines expected to be increased in patients with this hyperinflammatory disorder, including IL-6, TNF, IFNγ, and IL-18.[36]

Experimental evidence for neutrophil-mediated tissue injury in the pathobiology of HLH is also emerging. Splenic neutrophils from a mouse model of HLH upregulated the TREM1 protein and increased production of intracellular TNF, macrophage inflammatory protein (MIP)-1α (CCL3), MIP-1β (CCL4), and IL-1β. This phenotype was ameliorated with JAK1 and JAK2 inhibition (using ruxolitinib), but not IFNγ inhibition. Poorer survival of mice treated with IFNγ inhibition (compared with ruxolitinib) was rescued by the addition of neutrophil-depleting antibodies, but not anti-IL-6 or anti-TNF antibodies.[34,37] These data support a role for neutrophil activation in the pathobiology of HLH and highlight possible similarities between HLH-mediated organ injury and severe organ injury seen in other critical illnesses, such as sepsis and ARDS.[38,39]

Targeting GM-CSF in ARDS

The scientific rationale for targeting GM-CSF in patients with ARDS is gaining strength. The initial injury response or exudative phase of ARDS is characterised by release of potent proinflammatory mediators, including GM-CSF, monocyte chemoattractant protein 1 (CCL2), IL-1α, IL-8, and TNF secreted by resident alveolar macrophages, leading to recruitment of neutrophils and monocytes. Neutrophils have been strongly implicated in the development of ARDS[40] by acting as primary effector cells of bystander tissue injury through release of proteinases, reactive oxygen species, and neutrophil extracellular traps; recent reports have also highlighted the role of neutrophil extracellular traps in COVID-19.[41,42] Moreover, the extent, duration, and priming status of neutrophils in alveolar airspaces are strong predictors of outcome in ARDS.[25] Alveolar GM-CSF contributes to acute and persistent neutrophilic inflammation by affecting neutrophil function, including promoting upregulation of the IgA Fc receptor, formyl peptide receptor (FPR1), CD11b, and expression of the leukotriene B4 receptor; chemotaxis, phagocytosis, release of leukotriene B4 and arachidonic acid, NADPH oxidase 2 (CYBB)-mediated superoxide anion generation; and by exerting a pronounced pro-survival effect mediated by phosphoinositide 3-kinase (PI3K)-dependent inhibition of neutrophil apoptosis.[25,43–46] Recent study findings suggest that GM-CSF receptor alpha blockade can inhibit inflammation in response to inhaled lipopolysaccharide in a mouse model of acute lung injury.[47]

See Online for appendix

GM-CSF and COVID-19

The case for GM-CSF as a potential therapeutic target in patients with COVID-19-associated hyperinflammation and ARDS is also gaining strength, and several clinical trials are planned in patients with COVID-19, using agents that either target GM-CSF or its receptor (table). In COVID-19, a cytokine signature resembling secondary HLH (including increased G-CSF, IL-2, IL-7, IFNγ-inducible protein 10 [CXCL10], CCL2, CCL3, and TNF) is associated with disease severity.[14] Although, to the best of our knowledge, no data in bronchoalveolar lavage fluid have been published, serum levels of GM-CSF and G-CSF are upregulated in patients with COVID-19 compared with healthy volunteers, independent of intensive care status.[14] Evidence is also emerging that expansion of GM-CSF-expressing immune cells correlates with disease severity in COVID-19.[48] The percentages of GM-CSF-expressing $CD4^+$ T cells (Th1), $CD8^+$ T cells, natural killer cells, and B cells are significantly higher in the serum of patients with COVID-19 compared with healthy controls and patients with COVID-19 without critical illness.[48] $CD14^+$ $CD16^+$ inflammatory monocytes (rarely found in healthy controls) are raised in the peripheral blood of patients with COVID-19 and correlate with the extent of a severe pulmonary syndrome in the intensive care unit.[48] It seems plausible that GM-CSF potentially links the severe pulmonary syndrome-initiating capacity of pathogenic $CD4^+$ Th1 cells (GM-CSF-positive IFNγ-positive) with the inflammatory signature of monocytes ($CD14^+$ $CD16^+$ with high expression of IL-6) and their progeny in

patients with COVID-19.[48] GM-CSF could, therefore, serve as the integral link between Th1-driven acute lung injury and an autocrine loop of monocytes that further secrete GM-CSF and IL-6.[48] An alternative perspective is that rather than being pathogenic and causative of immunopathology, GM-CSF-positive lymphocytes could be responding to persistent viral replication and might indicate a potential protective role of GM-CSF in antiviral immunity in this disease context.

Inhibition of GM-CSF in COVID-19-associated hyperinflammation

Indirect evidence for a role for anti-GM-CSF therapeutic targeting in COVID-19-associated hyperinflammation comes from cytokine release syndrome following CAR T-cell therapy. The immunomodulatory agent tocilizumab (anti-IL-6-receptor monoclonal antibody) is licensed for treatment of cytokine release syndrome, a disorder that might be associated with neurotoxicity. Cytokine release syndrome is directly related to in-vivo T-cell expansion and striking production of the T-cell effector cytokines IL-6, TNF, CCL2, and GM-CSF. Current evidence suggests that serum levels of GM-CSF, ferritin, and IL-2 are associated with neurotoxicity.[49] Amounts of GM-CSF are raised in serum and cerebrospinal fluid in children with COVID-19 and CNS manifestations.[50] A proof-of-concept study using a neutralising anti-GM-CSF monoclonal antibody (lenzilumab) in a xenograft model prevented cytokine release syndrome and enhanced the efficacy of CAR T-cell therapy.[51] Based on these findings, a phase 2 trial combining lenzilumab in the setting of CAR T-cell therapy is planned. Next-generation CAR T cells in which GM-CSF has been knocked out by CRISPR-Cas9 gene editing are being developed to minimise the risk of cytokine release syndrome.[52]

In view of the central role of GM-CSF in several chronic inflammatory disorders, considerable interest has been shown in targeting this cytokine in hyperinflammatory disease contexts. Inhibition of GM-CSF or its receptor is currently being investigated in randomised trials in rheumatoid arthritis,[18] including a 24-week phase 3 head-to-head comparison trial in patients with rheumatoid arthritis (NCT04134728) aimed at inhibiting GM-CSF (otilimab), IL-6 (sarilumab), and the JAK-STAT pathway (tofacitinib). To the best of our knowledge, no overt safety concerns have been identified and there have been no cases reported of pulmonary alveolar proteinosis in the clinical development programmes of any agent targeting GM-CSF or its receptor to date. In the setting of severe COVID-19-associated hyperinflammation, a short duration of treatment with an anti-GM-CSF monoclonal antibody might be sufficient to switch off hyperinflammation while mitigating potential on-target safety concerns that could be associated with long-term GM-CSF blockade. It is also worth highlighting that GM-CSF induces the production of IL-6 and signals via the JAK-STAT pathway.[53] Clinical trials of JAK inhibitors are ongoing in patients with COVID-19 (eg, NCT04362137), and the IL-6 pathway is currently the focus of several clinical trials in COVID-19 (eg, NCT04320615). Interest in the IL-6 axis was probably fuelled by purported similarities (eg, increased C-reactive protein) between COVID-19-associated hyperinflammation and cytokine release syndrome associated with CAR T-cell therapy. Moreover, other agents used in secondary HLH (eg, IL-1 inhibition with anakinra)[54] are also currently being investigated in patients with COVID-19. Targeting GM-CSF could offer advantages over selective IL-6 blockade, because inhibition of GM-CSF might affect both hyperinflammation and ARDS, and might be less myelosuppressive and hepatotoxic than IL-6 blockade. JAK inhibitors are licensed for chronic inflammatory conditions (eg, rheumatoid arthritis) and myeloproliferative neoplasms and are being actively investigated in hyperinflammation.[55,56] However, the potential deleterious effects associated with inhibition of multiple cytokines simultaneously, compared with single-cytokine blockade, and potential increased risk of thrombosis requires careful consideration. This consideration is especially pertinent in the setting of COVID-19, in view of accumulating evidence of coagulopathy and autopsy findings of pulmonary microthrombi.[57]

Challenges of immunomodulation in COVID-19

The potential benefits of targeting GM-CSF in the context of a virally driven disorder such as COVID-19 need to be carefully balanced with potential risk associated with blocking the role of this cytokine in tissue homoeostasis, including maintenance of alveolar capillary barrier integrity[20] in host defence and epithelial repair. Rather than blocking GM-CSF, there is an opposing view that treatment with GM-CSF could have therapeutic potential in ARDS. In a proof-of-concept study, the beneficial effect of inhaled GM-CSF was shown in six patients with pneumonia-associated ARDS,[58] and a clinical trial is underway of administration of inhaled and intravenous recombinant GM-CSF (sargramostim) in patients with COVID-19 (NCT04326920). Evidence suggests that increased concentrations of GM-CSF in bronchoalveolar lavage fluid from patients with ARDS positively correlated with survival;[25] by contrast, a subsequent randomised trial of therapeutic administration of recombinant GM-CSF in ARDS (n=130) did not improve clinical outcomes.[59] In that study, administration of intravenous GM-CSF daily for 14 days was not associated with adverse clinical outcomes or increased concentrations of systemically measured cytokines, including IL-6, IL-8, TNF, or GM-CSF in bronchoalveolar lavage fluid (measured in selected participants).[59] These observations, together with studies showing that exogenous administration of GM-CSF does not exacerbate sepsis,[60] could provide a counter-argument for the approach of targeting GM-CSF in ARDS. First, as acknowledged by Paine and colleagues,[59] their study included a smaller than anticipated number of patients treated (the study

was originally designed with an enrolment target of 200, but recruitment proved slower than anticipated and the trial was closed after 132 participants had been enrolled) and the timing of treatment initiation might not have been ideal (ie, during the recovery phase of ARDS). Moreover, interventional studies with a GM-CSF antibody in COVID-19 are aimed at attenuating the immune dysregulation of hyperinflammation before it leads to the development of ARDS; once ARDS is established, it could indeed be too late for this intervention to provide substantial clinical benefit.

GM-CSF also has a highly context-dependent immunoregulatory role and can modulate dendritic cell differentiation to render them tolerogenic, which in turn leads to increased regulatory T-cell numbers and function.[61] Moreover, GM-CSF affects antiviral and antibacterial immunity and host defence,[62] so GM-CSF blockade could potentially compromise T-cell and B-cell recovery. Lymphopenia is an established risk factor for secondary bacterial infections and might predict fatality and worse outcomes in COVID-19.[2] In a cohort study of 54 non-survivors with confirmed COVID-19, approximately 50% had secondary bacterial infections.[12] Acquired impairment of neutrophil phagocytosis in critical illness predicts nosocomial infections and is reversed by GM-CSF ex vivo. However, administration of GM-CSF (sargramostim) in a randomised trial in this setting did not improve neutrophil phagocytosis.[63] There is also a theoretical possibility that immunomodulation in COVID-19 could represent a temporary reprieve and enable viral resurgence from a circulating reservoir of non-cleared virus. Strategies using antimicrobial prophylaxis (eg, with antibiotics or antiviral drugs) could be insufficient to mitigate the risk and could promote the development of resistant organisms. Additionally, it might be inappropriate to extrapolate experience (efficacy or safety profiles) of immunomodulation in hyperinflammation secondary to a drug-related trigger (eg, cytokine release syndrome after CAR T-cell therapy) or immunomodulation in chronic inflammatory disorders (eg, rheumatoid arthritis) to a viral setting, because a resident pool of virus could serve as a continuous stimulus for cytokinaemia, and immunomodulation might potentially affect viral clearance mechanisms. A deeper understanding of early pathophysiological events in viral (including COVID-19) or bacterial ARDS, or ARDS of other causes, will be imperative in our quest to develop novel therapeutic approaches and the role of anti-GM-CSF agents in these settings.

The pharmacodynamic effects of blocking IL-6 (antagonism directly with tocilizumab or indirectly with JAK inhibition and anti-GM-CSF monoclonal antibodies) could include rapid suppression of C-reactive protein and fever. These effects might not only make secondary infection or viral relapse difficult to detect, but also provide false reassurance of efficacy of the therapeutic agent, because these mechanistic effects might not always correlate with clinically meaningful outcomes.

Conclusions and future directions

Randomised trials are the gold standard to provide evidence for clinical decision making. However, since COVID-19 is a new disease entity, it presents several urgent challenges around clinical trial design, selection of patients, and stratification. Early intervention before the onset of respiratory failure will probably prevent poor outcomes.[64] Once patients need ventilatory support, the purported window of opportunity for therapeutic intervention might already have been missed, and patients might tip into an accelerated state, during which time initiation of treatment could be less effective or even futile[54] (figure 2). The ideal window of opportunity for immunomodulation might be before patients develop severe disease[64,65] and need invasive mechanical ventilation (intubation). However, robust predictive biomarkers for poor outcomes and in-depth characterisation of the host immune response across disease stages, to minimise the effect of immunomodulatory agents on the antiviral response, are urgently needed. Moreover, non-intubated patients would present a lower risk in terms of opportunistic or nosocomial infections, compared with intubated patients, who could have several artificial indwelling catheters (eg, endotracheal tubes, vascular access lines, or urinary catheters) that could act as a nidus for infection.

Strategies targeted at specific endotypes in ARDS are regarded as essential for optimum clinical outcomes. The apparent failure of large clinical trials in critical care has been attributed to inclusion of heterogenous non-stratified populations of patients. Reanalyses of clinical trials in both ARDS (statins)[66] and sepsis (anakinra)[67] have shown potential benefits in specific subgroups.

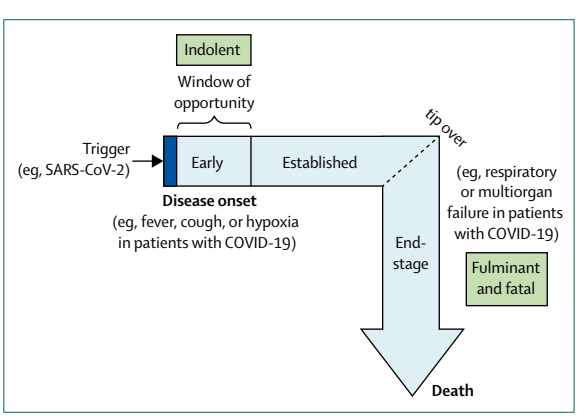

Figure 2: **A window of opportunity in hyperinflammation for optimum treatment intervention**

Hyperinflammation can be initiated by an inciting trigger (eg, SARS-CoV-2 infection) and can progress from an early indolent state to a fulminant and fatal hypercytokinaemia. Withholding potentially lifesaving immunomodulatory treatment until a patient is intubated could result in a missed window of opportunity for optimum therapeutic intervention. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Search strategy and selection criteria

We searched PubMed up to May 28, 2020, with the terms "GM-CSF", "haemophagocytic lymphohistiocytosis", "macrophage activation syndrome", "cytokine release syndrome", "COVID-19", "ARDS", and "acute respiratory distress syndrome" for full publications in the English language, with the aim of providing the scientific rationale and challenges of targeting granulocyte macrophage colony-stimulating factor (GM-CSF) in the context of haemophagocytic lymphohistiocytosis, acute respiratory distress syndrome, and COVID-19. We also searched ClinicalTrials.gov and Google to identify clinical trials and studies using therapies targeting GM-CSF or its receptor in COVID-19.

Identification of patients with COVID-19 who have a poor prognosis, with a modifiable clinical outcome, and who are most likely to benefit from immunomodulation will minimise exposure of patients with COVID-19 who could recover on their own to potential risks associated with immunosuppression. Identification of patients with COVID-19 using stratification variables is, however, very challenging without robust predictive biomarkers to identify those with poor prognosis who are likely to progress. It is important to maintain a measured clinical and scientific equipoise in the face of a rapidly evolving global pandemic. The bioethical stance of non-maleficence needs to be balanced against the risk of withholding potentially life-saving immunomodulatory treatment in a population with high mortality and few treatment options. Identification of new therapeutic approaches beyond existing licensed immunomodulatory agents would address potential issues about drug shortages for COVID-19 clinical trials, and for patients who are dependent on these drugs to control chronic conditions. Ongoing and future clinical trials will provide much needed evidence for safety and efficacy of immunomodulatory agents in this setting, and their results are eagerly awaited.

COVID-19 is a major global public health crisis with considerable mortality and morbidity, exerting inordinate pressure on health-care resources, including intensive care beds and ventilators. Cross-specialty collaboration and randomised trials will be essential to assess the effect of therapeutic blockade of GM-CSF on both hyperinflammation and ARDS, as well as host defence and potential risks in COVID-19. Early intervention with immunomodulation in patients identified by careful consideration of the benefit–risk profile might halt disease progression, obviate the need for mechanical ventilation, and reduce mortality in patients with COVID-19.

Contributors
PM and RCC drafted the report. All authors contributed to the discussion and revised and approved the report.

Declaration of interests
PM is a Medical Research Council (MRC)-GlaxoSmithKline EMINENT clinical training fellow with project funding outside of the submitted work; and receives co-funding by the National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre. IBM reports grants and personal fees from GlaxoSmithKline, during the conduct of the study. CS reports non-financial support from GlaxoSmithKline and grants from MedImmune, outside of the submitted work; and is Chief Investigator of a GlaxoSmithKline-sponsored clinical trial of otilimab, an anti-GM-CSF monoclonal antibody, in the setting of severe COVID-19. RCC reports grant funding from UK Research and Innovation MRC, and NIHR ULCH Biomedical Research Centre, and institutional research collaboration funding from GlaxoSmithKline, during the conduct of the study. PJMO reports personal fees for consultancy work with Janssen, Johnson & Johnson, and Sanofi; grants from MRC, EU, NIHR Biomedical Research Centre; collaborative grants with GlaxoSmithKline; and an NIHR Senior Investigator Award; all outside of the submitted work. JCP, JJM, and JDI declare no competing interests.

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