Editorial

Weathering the Cytokine Storm in Susceptible Patients with Severe SARS-CoV-2 Infection

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High-risk patients requiring hospitalization for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are those over 60 years old, males, obese, smokers, and those with common comorbidities including hypertension, cardiovascular disease, diabetes, and chronic lung disease.[1] Immunocompromised and cancer patients are also at greater risk. In one meta-analysis, the relative risk for experiencing severe versus nonsevere COVID-19 disease was 58%, 59%, and 71% higher in patients with hypertension, respiratory disease, and cardiovascular disease, respectively.[1] Use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for hypertension, heart failure, and diabetes may upregulate expression of ACE2, the latter being involved in the binding and uptake of SARS-CoV-2 to the lung epithelium.[2] ACE2 may also be unregulated by smoking in small airway epithelia.[3] It remains unclear whether the increased risk of COVID-19 infection is attributable to hypertension or age-related comorbidity *per se*. Current hypertension or heart failure guidelines do not advocate stopping or switching ACE inhibitors or ARBs.

Upstream therapeutic strategies revolve around the use of antivirals (Figure 1). One study showed no benefit in using lopinavir plus ritonavir over standard of care for sick hospitalized adult patients with severe COVID-19 pneumonia even though the study was likely underpowered.[4] This in turn perhaps infers that using upstream antiviral therapy alone may not be successful later on in the disease process once the downstream cytokine avalanche has been triggered, resulting in subsequent lung damage. Having said that compassionate use of iv remdesivir in 53 patients with severe COVID-19 infection resulted in 68% having improved oxygenation status and 18% mortality among those receiving invasive ventilation, albeit with no control arm for comparison.[5] There has also been interest in using azithromycin for COVID-19. It has been included in the ACTION (NCT04332107) and HyAzOUT (NCT04334382) trials on the basis of its immunomodulatory and putative antiviral activity, although its effects on SARS-CoV-2 remains speculative.[6] Caution is advised in trials evaluating azithromycin in conjunction with hydroxychloroquine (NCT04335552), due to potential additive effects on QT interval prolongation and propensity for arrhythmias.

Blocking viral host cell entry with the antimalarial drugs hydroxychloroquine or chloroquine is another potential upstream modality (Figure 1). Hydroxychloroquine is safer and more potent in terms of *in vitro* SARS-CoV-2 suppression.[7,8] Hydroxychloroquine acts via ACE2 and increases endosomal pH to attenuate SARS-CoV-2 endocytic host cell entry into the lung epithelium. Hydroxychloroquine has shown some promising preliminary clinical results in terms of attenuating *in vivo* SARS-CoV-2 viral load[6] and has been included in the WHO SOLIDARITY trial as well as the NIHR RECOVERY and PRINCIPLE trials. Hydroxychloroquine may also exhibit downstream immunosuppressive effects by reducing IL-6 production from T cells and monocytes,[9] which may explain in part its use in autoimmune conditions. To date one non peer reviewed randomised controlled trial from France with hydroxychloroquine added to usual care in 181 patients with severe COVID-19 pneumonia reported no significant impact on the primary end point of intensive care or death within 7 days, while 9.5% of patients had to stop hydroxychlorquine due to QT prolongation. Bromhexine is an over-the-counter cough remedy that blocks receptor-mediated viral cell entry via the transmembrane protease, serine 2 enzyme (TMPRSS2).[10] Theoretically, there could be potential synergy in terms of more effectively blocking viral host cell entry using combined hydroxychloroquine and bromhexine (NCT04340349), but at present this only remains speculative. It remains to be seen whether such agents are more likely to be effective early on in COVID-19 disease given that they prevent upstream viral entry.

Little consideration appears to have been given to susceptible patients with obstructive airways disease with regard to COVID-19 infection. In particular, elderly patients with chronic obstructive pulmonary disease (COPD) have impaired respiratory reserve and a plethora of comorbidities, which potentially confers both pathophysiological and pharmacological susceptibility. Such individuals are at high risk of adverse outcomes as a result of severe SARS-CoV-2 infection. Patients with COPD taking inhaled corticosteroid (ICS) combination therapy have an increased pneumonia risk, especially with

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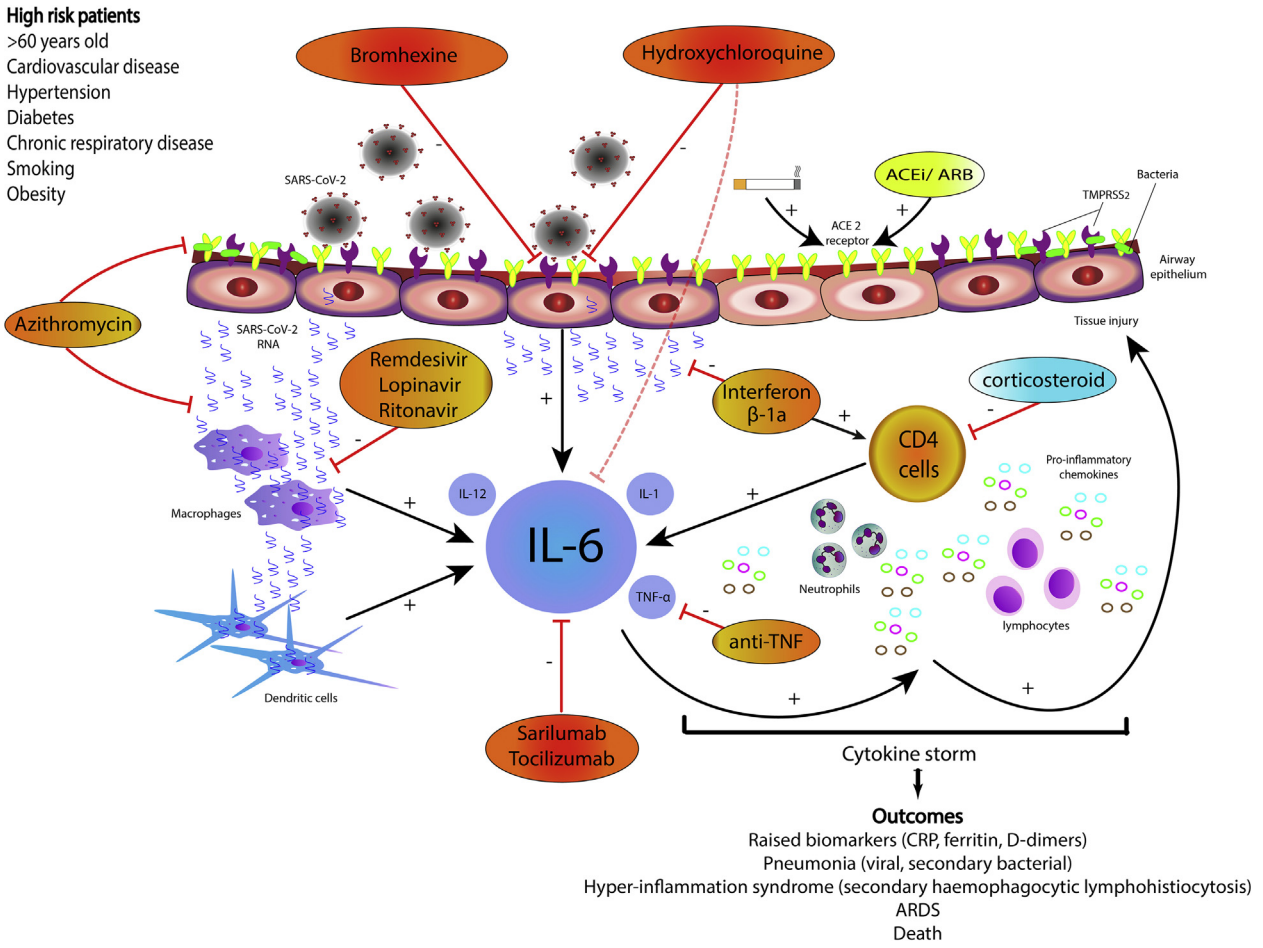

FIGURE 1. The cytokine cascade resulting from acute severe SARS-CoV-2 infection, with downstream IL-6 activation considered to be a hallmark feature in terms of progression of COVID-19 pneumonia to hyperinflammation and ARDS. Also shown are the putative mechanisms of action for bromhexine and hydroxychloroquine in attenuating upstream SARS-CoV-2 tissue binding, the effect of antivirals on replication, azithromycin as an antiviral and immunomudulator, nonspecific cytokine suppression by corticosteroids, together with the selective downstream effect of IL-6 blockade with tocilizumab or sarilumab and effects of anti-TNF and interferon beta-1-a. *ACE2*, Angiotensin converting enzyme 2; *ACEI*, angiotensin converting enzyme inhibitor; *ARB*, angiotensin II receptor blocker; *ARDS*, acute respiratory distress syndrome; *CRP*, C reactive protein; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2; *TNF*, tumour necrosis factor; *TMPRSS2*, transmembrane protease, serine 2.

lipophilic drugs such as fluticasone furoate,[11] due to its prolonged lung retention and associated local immunosuppression in the presence of altered lung microbiome and impaired mucociliary clearance.[12] Moreover, suppression of interferon by fluticasone propionate is associated with an increased bacterial load after rhinovirus infection.[13] Corticosteroids may also attenuate production of the antibacterial protective peptide cathelicidin in the lung epithelium.[14] Thus, secondary bacterial infection might contribute to the cumulative inflammatory burden in addition to viral pneumonia. Caution should be exercised in extrapolating from COPD to asthma, even though up to 20% of patients with COPD have a corticosteroid responsive eosinophilic component. Hence, in patients with COPD with blood eosinophils $\geq$300 cells/μL, the benefit of fluticasone furoate in reducing severe exacerbations outweighs its risk in inducing severe pneumonia.[15] Nevertheless, one Canadian cohort study of patients with asthma demonstrated that current ICS use was associated with a 45% relative increased risk of pneumonia, amounting to an excess of 1.44 cases per 1000 patient-years.[16]

Interestingly, ciclesonide and mometasone, but not budesonide, beclomethasone, or fluticasone, exhibit *in vitro* suppression of SARS-CoV-2 replication to a similar degree as lopinavir, albeit in preliminary non peer reviewed data.[17] For ciclesonide, its target on viral replication appears to be nonstructural protein 15 (NSP15). Budesonide and formoterol independently suppress systemic suppression of IL-6 in relation to acute lung injury in the mouse model.[18] Pointedly, asthmatics taking ICS are 49% less likely to have a severe outcome after hospitalization for influenza A/H1/N1 infection,[19] perhaps inferring a generic protective ICS class effect. In the meantime, the key message for patients with asthma is to adhere to their ICS controller therapy as this is likely to offer the best protection against any viral insult including SARS-CoV-2. At this juncture, no evidence can support switching patients with controlled asthma to inhaled ciclesonide or mometasone. A study evaluating ciclesonide in South

Korea will look at the rate of SARS-CoV-2 eradication in patients with mild COVID-19 infection (NCT04330586). Another study comparing high dose ciclesonide with usual care from Japan will report on progression of severe COVID pneumonia.

Corticosteroids may be considered as a rather blunt tool for dealing with the cytokine cascade in COVID-19 infection as they exhibit a broad-spectrum suppressive effect. Systemic corticosteroids are part of the routine management of acute viral exacerbations of asthma and COPD and are effective at treating the eosinophilic component of type 2 inflammation.[20] Corticosteroids may also suppress host immune responses and increase viral replication that is reversed by adjuvant interferon.[21] A study with inhaled interferon-beta-1a (SNG001) will evaluate whether upregulating lung antiviral defenses is effective in COVID-19 illness, whereas other trials will evaluate subcutaneous interferon-beta-1a with lopinavir/ritonavir (NCT04315948). One might postulate that nebulized interferon-beta-1a may not achieve adequate alveolar drug concentrations in severe COVID-19 infection because by the same token nebulized antibiotics are not effective in bacterial pneumonia.

SARS-CoV-2 infection may induce a profound downstream cytokine cascade involving IL-1β, IL-6, IL-12, and TNF-α (Figure 1).[22] This release of cytokines is followed by rapid development of lung tissue damage resulting in acute respiratory distress syndrome, sepsis, and organ failure, which may require assisted ventilatory support and extracorporeal membrane oxygenation. One non peer reviewed study in severe COVID-19 infection found that the risk of respiratory failure in patients with maximal circulating IL-6 levels >80 pg/mL was 22-fold higher with a median time to mechanical ventilation of 1.5 days.[23]

A more selective approach is therefore required to address the downstream cytokine storm. Recent attention has centered around the possibility of therapeutic intervention with anti-IL-6 drugs such as tocilizumab and sarilumab that are indicated for rheumatoid disease. There is emerging evidence that they may also be useful when repurposed for severe SARS-CoV-2 infection in terms of dampening the downstream cytokine response and the associated hyperinflammatory syndrome, the latter primarily characterized by secondary hemophagocytic lymphohistiocytosis.

A compassionate use uncontrolled non peer reviewed study from China in 21 patients infected with SARS-CoV-2 using the anti-IL-6 agent tocilizumab showed a rapid reduction in fever, C reactive protein (CRP), and oxygen requirement along with improved radiological appearances and normalization of lymphocyte counts within 5 days of administration of a single 400 mg dose.[24] Moreover, 90% of patients were discharged within a mean hospitalization period of 13.5 days after tocilizumab. All patients already had routine treatment for 1 week including lopinavir and methylprednisolone before receiving tocilizumab. A significant limitation may therefore be survival bias in that sicker patients would be expected to have rapidly deteriorated within the first week of hospitalized illness. Evidently, these data need urgent replication ideally in randomized controlled trials. A study is now under way recruiting hospitalized patients with SARS-CoV-2 (NCT04315298) using the anti-IL-6 agent sarilumab, whereas 3 other studies are evaluating tocilizumab alone: COVACTA (NCT04320615) and TOCOVID (NCT04322773), or in combination with favipiravir (NCT04310228) as well in the NIHR RECOVERY trial as part of the second randomization arm. We would advocate that patients with severe COVID-19 infection should be screened for biomarkers of hyperinflammation including rising CRP, ferritin, D-dimer, plasma viscosity, and cytopenia including falling platelet count, as these may highlight at-risk patients where IL-6 suppression could be beneficial.

There are cogent reasons to suggest that a combined treatment modality might be required to obviate upstream SARS-CoV-2 lung tissue binding with hydroxychloroquine or bromhexine, or instead with antivirals, together with downstream IL-6 blockade by sarilumab or tocilizumab (Figure 1). With this in mind we believe studies are urgently warranted to investigate such combination therapy in older susceptible individuals with comorbidities who are at high risk for developing severe COVID-19 pneumonia. Ultimately, the indications for such combined therapies will be determined by factors such as stage of disease, safety, cost, and route of administration.

KEY LEARNING POINTS

- Severe SARS-CoV-2 infection with poor outcomes occurs in older susceptible patients who may be male, obese, smokers, and with multiple comorbidities.
- Patients with eosinophilic asthma and COPD should continue to use ICS-containing therapy to maintain optimal control and protect against viral insults including SARS-CoV-2 infection.
- Strategies including antiviral therapy such as lopinavir-ritonavir or blocking viral host cell entry with hydroxychloroquine may not be successful unless used earlier in the course of COVID-19 infection.
- More severe COVID-19 infection may produce a cytokine storm associated with hyperinflammatory syndrome and hemophagocytic lymphohistiocytosis, with IL-6 levels being highly predictive of respiratory failure.
- Screening for biomarkers of hyperinflammation such as cytopenia, CRP, D-dimer, plasma viscosity, and ferritin may identify at-risk patients where cytokine suppression may be beneficial.
- Clinical trials are urgently warranted to evaluate a combined therapeutic strategy to target upstream and downstream pathways in severe COVID-19 disease.

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