COVID-19: consider cytokine storm syndromes and immunosuppression

As of March 12, 2020, coronavirus disease 2019 (COVID-19) has been confirmed in 125 048 people worldwide, carrying a mortality of approximately 3.7%,1 compared with a mortality rate of less than 1% from influenza. There is an urgent need for effective treatment. Current focus has been on the development of novel therapeutics, including antivirals and vaccines. Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome. We recommend identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality.

Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality.2 Secondary haemophagocytic lymphohistiocytosis (sHLH) is an under-recognised, hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure. In adults, sHLH is most commonly triggered by viral infections3 and occurs in 3.7–4.3% of sepsis cases.4 Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients.5 A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterised by increased interleukin (IL)-2, IL-7, granulocyte colony stimulating factor, interferon-γ-inducible protein 10, monocyte chemotactic protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α.6 Predictors of fatality from a recent retrospective, multicentre study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (mean 1297.6 ng/ml in non-survivors vs 614.0 ng/ml in survivors; p<0.001) and IL-6 (p<0.0001),2 suggesting that mortality might be due to virally driven hyperinflammation.

As during previous pandemics (severe acute respiratory syndrome and Middle East respiratory syndrome), corticosteroids are not routinely recommended and might exacerbate COVID-19-associated lung injury.7 However, in hyperinflammation, immunosuppression is likely to be beneficial. Re-analysis of data from a phase 3 randomised controlled trial of IL-1 blockade (anakinra) in sepsis, showed significant survival benefit in patients with hyperinflammation, without increased adverse events.8 A multicentre, randomised controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in patients with cytokine storm syndromes and immunosuppression.

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COVID-19 pneumonia and elevated IL-6 in China (ChiCTR2000029765).\textsuperscript{3} Janus kinase (JAK) inhibition could affect both inflammation and cellular viral entry in COVID-19.\textsuperscript{10} All patients with severe COVID-19 should be screened for hyperinflammation using laboratory trends (eg, increasing ferritin, decreasing platelet counts, or erythrocyte sedimentation rate) and the HScore\textsuperscript{5} (table) to identify the subgroup of patients for whom immunosuppression could improve mortality. Therapeutic options include steroids, intravenous immunoglobulin, selective cytokine blockade (eg, anakinra or tocilizumab) and JAK inhibition. PM is a clinical training fellow within the Experimental Medicine Initiative to Explore New Therapies network and receives project funding unrelated to this Correspondence. PM also receives co-funding by the National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre. DFM chairs the NIHR and Medical Research Council funding committee for COVID-19 for therapeutics and vaccines. DFM reports personal fees from consultancy for ARDS for GlassSmithKline, Boehringer Ingelheim, and Bayer; in addition, his institution has received funding from grants from the UK NIHR, Wellcome Trust, Innovate UK, and others, all unrelated to this Correspondence. DFM also has a patent issued to his institution for baricitinib-1 receptor blockade. All other authors declare no competing interests.

Puja Mehta, Daniel F McAuley, Michael Brown, Emilie Sanchez, Rachel S Tattersall,* Jessica J Manson, on behalf of the HLH Across Speciality Collaboration, UK

jessica.manson@nhs.net

Centre for Inflammation and Tissue Repair, UCL Respiratory, Division of Medicine, University College London, London, UK (PM); Department of Rheumatology (JJM), Hospital for Tropical Diseases (MB), and Department of Clinical Virology (ES), University College London Hospital, London NW1 2PG, UK; Welcome-Wolfson Institute for Experimental Medicine, Queen’s University Belfast, Belfast, UK (DFM); Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, UK (DFM); Department of Rheumatology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (RST); and Sheffield Children’s Hospital NHS Foundation Trust, Sheffield, UK (RST).


