Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

also calculated the proportion of patients who fulfilled a novel consensus-driven definition of low disease activity in diffuse cutaneous systemic sclerosis,[10] comprising mRSS of 10 or lower, HAQ-DI of 0·75 or less, and patient global assessment of 3 or less (on a 0–10 scale). During the double-blind phase of ASSET, 15–16% of patients reached low disease activity status in both study groups.[5] Nevertheless, at month 18, this proportion rose to 31% in the abatacept–abatacept group compared with 13% in the placebo–abatacept group.[6] Since low disease activity is a categorical endpoint, its use could complement continuous endpoints such as ACR CRISS. It is encouraging to note that low disease activity and ACR CRISS moved in the same direction. A higher proportion of patients on abatacept than on placebo achieved ACR CRISS of 0·6 or greater in both the double-blind phase (55% *vs* 36%)[5] and the open-label extension (66% abatacept–abatacept *vs* 50% placebo–abatacept).[6] Chung and colleagues acknowledge this finding as indirect evidence of a late clinical effect of abatacept, and it offers the first insight into the time needed to reach low disease activity in early diffuse cutaneous systemic sclerosis. This notion, together with knowledge of dynamics of fibrotic damage in systemic sclerosis, suggests that we should start to consider longer trial durations to better appreciate treatment effects in diffuse cutaneous systemic sclerosis.

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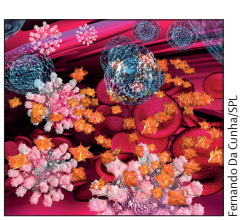
Defining the scourge of COVID-19 hyperinflammatory syndrome

It is abundantly clear that a subset of patients admitted to hospital with COVID-19 develop hyperinflammatory complications of severe COVID-19 infection or cytokine storm syndrome,[1,2] which is frequently fatal. What is less clear is how to define the cytokine storm syndrome in the context of severe COVID-19 infection. In *The Lancet Rheumatology*, Webb and colleagues[3] propose a set of clinical criteria for COVID-19-associated hyperinflammatory syndrome (cHIS). Development of such criteria are critically important for clinical trial enrolment and for aiding clinicians in recognising patients who will benefit from therapy targeting the cytokine storm syndrome associated with COVID-19.

One of the silver linings of the COVID-19 pandemic is the attention brought to cytokine storm syndromes in general. Cytokine storm syndrome refers to an umbrella of clinical states in which hyperinflammation and multiorgan disease arise from excessive cytokine release due to uncontrolled immune activation, and includes infectious, rheumatic, oncological, and immunotherapeutic aetiologies responsible for mortality in children and adults all over the world. Despite this, cytokine storm syndromes are frequently under-recognised,[4] and the evidence base for treatment is lacking. There are both broad cytokine storm syndrome criteria and disease-specific cytokine storm syndrome criteria (appendix), none of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which is perfectly sensitive or specific, thus adding to the complexities and difficulties in defining and diagnosing cytokine storm syndrome. The cytokine storm syndrome associated with COVID-19 is relatively unique among infectious cytokine storm syndromes with a propensity for early lung involvement in the form of acute respiratory distress syndrome and a predilection for clotting, as well as increased but less marked elevations in serum ferritin and interleukin-6 (IL-6) concentrations compared with other cytokine storm syndromes.[5] To establish criteria specific to COVID-19, Webb and colleagues did a systematic review of clinical and laboratory parameters linked to cHIS and compared those with other disease-associated cytokine storm syndrome criteria, particularly the 2016 systemic juvenile idiopathic arthritis macrophage activation syndrome criteria (appendix).[6] This approach lends credence to the concept that various hyperinflammatory syndromes triggered by different aetiologies, although not identical, share similar features and can be usefully categorised under the umbrella term of cytokine storm syndrome.[5]

Webb and colleagues report that meeting two or more cHIS criteria place patients with COVID-19 at increased risk of mortality and requiring invasive mechanical ventilation (odds ratio 1·6 [95% CI 1·2–2·1], p=0·0020, for mortality and 4·3 [3·0–6·0], p<0·0001, for mechanical ventilation).[3] The cHIS score also correlates with severity of oxygen requirement and risk for clinical deterioration of people with severe COVID-19. This finding is important for early recognition of patients with COVID-19 cytokine storm syndrome who might benefit from immunomodulatory or immunosuppressive approaches to treat the syndrome.[5] The rapidly changing approach to COVID-19 management, including the early initiation of glucocorticoids[7] during hospital admission, will probably modify components of the cHIS criteria, such as the presence of fever. This mirrors previous experience in children with systemic juvenile idiopathic arthritis in which IL-1 and IL-6 blocking biological treatments diminished the sensitivity of systemic juvenile idiopathic arthritis macrophage activation syndrome criteria.[8] As knowledge about COVID-19 grows, evidence from a full range of medical specialties will need to be assimilated to further define and categorise the role of hyperinflammation and cytokine storm syndrome in COVID-19 mortality and morbidity.

One approach for diagnosing cytokine storm syndrome in general has been to simplify criteria for early recognition of cytokine storm syndrome in the setting of febrile individuals admitted to hospital based largely on hyperferritinaemia.[9] Indeed, algorithms in our own hospitals support obtaining ferritin on all patients admitted to hospital with COVID-19 to help identify signs of cytokine storm syndrome. Whether or not this reductionist methodology will be of value for COVID-19 cytokine storm syndrome remains to be seen. Moreover, there will probably need to be successive iterations of the cHIS criteria to best define those who will benefit from treatment that targets cytokine storm syndromes in the context of ongoing developments in standard of care. Currently, clinicians worldwide are reliant on a collaborative approach of colleagues in various subspecialties who recognise or diagnose and treat various cytokine storm syndromes. A multidisciplinary team of intensivists, pulmonologists, haemato-oncologists, infectious disease experts, and paediatric and adult rheumatologists, among others, can be beneficial for aiding people with COVID-19 hyperinflammation in particular and to build on cytokine storm syndrome expertise in general. Perhaps, geneticists will be valuable as well in the near future, as we learn the genetic predispositions for cytokine storm syndrome development in the setting of infections and other triggers of disease.[10]

For now, Webb and colleagues are the first to report cytokine storm syndrome clinical criteria specific to COVID-19 in the form of cHIS.[3] Importantly, these criteria are relatively standard assessments that are readily available, timely, and not cost-prohibitive for most countries. These criteria will need validation, but for now, should help clinicians to recognise cytokine storm syndrome in the setting of COVID-19 for early initiation of potentially life-saving immunotherapy.

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The opening salvo of anti-complement therapy against COVID-19

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The COVID-19 pandemic remains unrelenting as the autumn of 2020 approaches. Despite many clinical trials underway to find effective treatments for COVID-19, few studies have yielded positive results. Increasing evidence shows diffuse activation of the complement pathway in severe COVID-19 infections, from increased serum levels to widespread deposition in autopsy specimens.[1–4] Initial case reports and case series using complement inhibitors in COVID-19 have shown promising results.[5–8] The complement pathway, a key effector of the innate immune system, has emerged as a nidus of investigation in this pandemic.[9]

In brief, the complement cascade can be activated by three pathways (classical, lectin, and alternative), which converge on the terminal complement pathway at C3. The terminal pathway results in anaphylatoxins, C3a and C5a, and the membrane attack complex (MAC), C5b-9. The anaphylatoxins are potent activators of neutrophils and monocytes. The MAC disrupts pathogen cell membranes. The dysregulation of this pathway is hypothesised to underlie severe COVID-19 complications.

In *The Lancet Rheumatology*, Alexander Vlaar and colleagues[10] report the first randomised controlled clinical trial investigating a complement pathway inhibitor for severe COVID-19. 30 patients (22 [73%] men and eight [27%] women) were randomly assigned to receive IFX-1, an investigational drug that inhibits C5a (n=15), or standard of care (n=15). The primary endpoint of mean relative change in the ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air (PaO_2/FiO_2) on day 5 was not significantly different between groups (difference –24% [95% CI –58 to 9], p=0·15). The heterogeneity of oxygenation levels in COVID-19 made this a problematic endpoint, as the authors discuss. Nevertheless, the trial shows the safety and tolerability of IFX-1 in patients with severe COVID-19—an important milestone.

The secondary outcomes reported are notable. In IFX-1-treated patients, there were fewer pulmonary embolisms (two [13%] patients in the IFX-1 group *vs* six [40%] in the control group) and fewer cases of renal impairment (none *vs* two) than in the control group. The IFX-1 group had a significantly lower estimated 28-day mortality rate versus the control group (adjusted hazard ratio for death 0·65 [95% CI 0·10–4·14]). This small exploratory study does not have enough power to draw conclusions about these endpoints, but data certainly are hypothesis generating.

An important caveat is that pharmacokinetic and pharmacodynamic analysis, including C5a, are absent in this study and are planned to be published separately. Investigators using the C5 complement pathway inhibitors eculizumab and ravulizumab have significantly increased their dose and dosing frequency in the acute setting of COVID-19 compared with the doses approved for use in atypical haemolytic uremic syndrome. Whether IFX-1 in this trial successfully inhibited complement C5a in the setting of severe COVID-19 is uncertain at this time.

The next step for IFX-1 is proceeding with the phase 3 trial, informed by the trial by Vlaar and colleagues. The randomised, placebo-controlled, phase 3 trial aims to enrol 360 patients with COVID-19 who have been intubated less than 48 h, with 28-day all-cause mortality as the primary endpoint.