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.

Canakinumab in a subgroup of patients with COVID-19

In a subgroup of patients, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces a hyperinflammatory response that leads to acute respiratory distress syndrome.[1] SARS coronaviruses have been shown to trigger the inflammasome and the release of interleukin-1β (IL-1β).[2]

We did a retrospective analysis of ten patients (nine white men and one white woman) with confirmed SARS-CoV-2 infection, bilateral pneumonia, hyperinflammation (defined as serum C-reactive protein ≥50 mg/L), and respiratory failure (requiring supplemental oxygen without invasive ventilation). These patients were treated with canakinumab, a human monoclonal antibody against IL-1β, administered subcutaneously in a single 300 mg dose, in April, 2020, at the Infectious Disease Clinic of SS. Annunziata Hospital in Chieti, Italy (appendix pp 1–8). All patients also received hydroxychloroquine (200 mg twice daily) and lopinavir–ritonavir (400 mg twice daily of lopinavir and 100 mg twice daily of ritonavir). The patients provided written informed consent for the off-label use of the drugs. The patients' baseline characteristics can be found in the appendix (pp 1, 4).

Canakinumab was well tolerated, with no recorded injection site reactions or systemic adverse events. Canakinumab administration was associated with a rapid and significant reduction in serum C-reactive protein at day 1 and day 3 and an improvement in oxygenation, with the PaO_2:FiO_2 ratio increasing between baseline and day 3 and day 7 after treatment (appendix pp 2, 7–8). At 45 days after hospitalisation, all ten patients were alive and discharged from hospital without physical limitations caused by COVID-19 or the need for oxygen therapy (appendix p 3). Notably, none of the patients developed neutropenia or bacterial sepsis.

For an indirect comparison, we selected the first ten patients with confirmed SARS-CoV-2 infection, bilateral pneumonia, hyperinflammation, and respiratory failure (requiring supplemental oxygen without invasive ventilation) who were hospitalised at our centre in March, 2020. These patients received hydroxychloroquine and lopinavir–ritonavir, but not canakinumab. By contrast to the patients treated with canakinumab, the patients not treated with canakinumab showed slower improvements in serum C-reactive protein and PaO_2:FiO_2 ratio (appendix pp 5, 8). At 45 days after hospitalisation, one patient had died, nine patients had been discharged from hospital, and one of the nine discharged patients required oxygen therapy (appendix p 6).

To our knowledge, these data, although preliminary, are the first to describe the use of canakinumab to treat patients with COVID-19. Canakinumab is an IL-1 blocker approved for the treatment of juvenile rheumatoid arthritis and other chronic autoinflammatory syndromes. Cavalli and colleagues[3] reported on the efficacy of another IL-1 blocker, intravenous anakinra (5 mg/kg twice daily), which also rapidly reduced serum C-reactive protein, improved oxygenation, and, when compared with a matched cohort, was associated with improved survival. Our observations add further evidence to support the central role of IL-1β in the pathophysiology of COVID-19. Although anakinra functions as a receptor antagonist that blocks the activity of both IL-1β and IL-1α, canakinumab selectively blocks the IL-1β that is generated within the inflammasome.[4] The rapid improvement in serum inflammatory biomarkers after the administration of canakinumab therefore implicates the IL-1β inflammasome pathway in the pathophysiology of COVID-19.

Notwithstanding the many limitations of these initial data, such as the small sample size and the absence of a random comparison, these data represent the first available description of the use of canakinumab to treat COVID-19 and show a rather favourable safety and efficacy profile that would be considered encouraging if compared with other published cohort studies.[3,4] Canakinumab is already commercially available. When tested in patients with cardiovascular disease, a group that is at a particularly high risk for COVID-19-related mortality, canakinumab significantly reduced the incidence of atherothrombotic events and heart failure exacerbations, which is another potential benefit.[5]

In conclusion, in ten hospitalised adult patients with COVID-19, bilateral pneumonia, hyperinflammation, and respiratory failure who did not require mechanical ventilation, 300 mg of subcutaneous canakinumab was safe, well tolerated, and associated with a rapid reduction in the systemic inflammatory response and an improvement in oxygenation.

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See Online for appendix

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See **Online** for appendix

Pulmonary intravascular coagulopathy in COVID-19 pneumonia

We read with pleasure the thoughtful Viewpoint by Dennis McGonagle and colleagues[1] on lung immunothrombosis during infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, some of the key pathogenetic events were not highlighted by the authors.

Evidence from the early stages of disease suggest the occurrence of diffuse alveolar damage with infiltrating multinucleated cells and few macrophages.[2] CT perfusion scans done in patients with early pneumonitis reveal microangiopathy that presents as hypoperfusion of the involved parenchyma (appendix). McGonagle and colleagues cite a study in which single-cell analysis showed no angiotensin-converting enzyme 2 (ACE2) expression in endothelial cells or alveolar macrophages.[1] However, other studies showed ACE2 expression in vascular endothelial cells in the lungs during infection with severe acute respiratory syndrome coronavirus (SARS-CoV),[3] or in the kidney during SARS-CoV-2 infection,[4] supporting the hypothesis that there is a receptor in all endothelial cells at the systemic level.

By infecting endothelial cells, the virus could alter the cells' function from the inside, as happens for other viruses. McGonagle and colleagues note that endothelial cells indeed express ACE2. The microangiopathy seen in patients with COVID-19 might therefore arise both from the inside (endothelial cells) and from the outside (platelets, cytokines, neutrophil extracellular traps, thrombophilic factors), resulting in, what we call endothelial leuko-thrombo-inflammation.

Alveolar haemorrhage can also occur in COVID-19 and an autopsy series from the USA showed foci of haemorrhage in all but one patient plus diffuse alveolar damage and mild-to-moderate infiltrates of CD4+ and CD8+ lymphocytes; CD4+ T cells were seen in aggregates around small blood vessels, some of which appeared to contain platelets and small thrombi. In addition, fibrin thrombi were present within the capillaries and small blood vessels with entrapment of numerous neutrophils. Neutrophil extracellular traps have been observed in the advanced phases of lung inflammation and one preprint paper reported the presence of CD61+ megakaryocytes.[5] Since platelets are normally produced in the lung, the thrombotic events are certainly facilitated. However, it is crucial to recall the hierarchical role of endothelial cells, which appear to be central regulators of the cytokine storm. In models of viral post-influenza inflammatory storms in the lung, triggering sphingosine-1-phosphate ($S1P_1$) receptors, which are expressed on endothelial cells and lymphocytes in the lung, suppressed cytokine production, innate immune cell recruitment, and cytokine release syndrome,[6] thereby decreasing lethality. Clinically, this finding could mean that, failing effective antiviral therapy (eg, remdesivir), treatments aimed at suppressing cellular aggregation or neutrophil extracellular trap formation and triggering $S1P_1$ signalling (eg, fingolimod) could be crucial in curtailing the endothelial leuko-thromboinflammatory storm before it starts, thus reducing the high mortality rate observed in patients with COVID-19 treated in intensive care units.

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We read with interest the Viewpoint by Dennis McGonagle and colleagues.[1] To account for unusual clinicopathological features of COVID-19 disease, particularly coagulopathy, the authors point to dysregulated immunity and systemic inflammation reminiscent of a cytokine storm or macrophage activation syndrome (MAS). Although the authors' contribution comes down firmly on the immunological side of the debate over whether COVID-19 coagulopathy is due principally to immune or endothelial dysfunction,[2] the common background assumption to both sides is that modelling COVID-19 using previously described clinical syndromes and traditional pharmacological and physiological mechanisms will lead to deeper insights into the disease.