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Mounting evidence of impaired viral control in severe COVID-19

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Substantial gaps in knowledge regarding the evolution and pathogenesis of COVID-19 remain after 1 year of the SARS-CoV-2 pandemic. At the start of the pandemic, a biphasic model to explain the physiopathology of COVID-19 became popular. This model divided the disease course into an initial viral response phase, followed by the inflammatory response phase.[1,2] In the inflammatory response phase, the virus is thought to have a minor role, and host inflammatory responses are the predominant mediators of pathophysiology, by triggering tissue damage leading to acute respiratory distress syndrome.[1,2] Growing evidence from our group and others suggest that this model might need revising. Patients with the most severe forms of the disease show the highest viral RNA loads in respiratory samples[3] and prolonged viral shedding.[4] Most critically ill patients with COVID-19 show SARS-CoV-2 RNAaemia, with viral RNA load in plasma correlating with the degree of severity and the risk of mortality.[5,6] Non-survivors show more frequent antigenaemia.[6] Furthermore, autopsies from COVID-19 patients demonstrate viral dissemination by the presence of viral particles and viral RNA in different organs.[7] All these findings suggest that the virus is a key driver of pathogenesis in severe COVID-19. Some immunological signatures denote an impaired ability to control viral replication in patients with severe COVID-19; in critically ill patients, absent or insufficient specific anti-SARS-CoV-2 S antibodies correlate with the presence of antigenaemia, high viral RNA loads in plasma, and mortality.[6] Patients with severe COVID-19 also show impaired interferon type I response, which is associated with a persistent blood viral load (appendix p 1).[8]

Although inflammation appears to be a central pathogenic event in severe COVID-19 (as demonstrated by the success of steroids and interleukin (IL)-6 pathway blockers in clinical trials),[9] we should not forget what drives the inflammatory process in these patients. Our results show a direct correlation between the concentrations of viral RNA in plasma and those of pro-inflammatory cytokines (C-X-C motif chemokine ligand 10, monocyte chemoattractant protein-1, IL-6, IL-15, and granulocyte-macrophage colony-stimulating factor) and anti-inflammatory or immunosuppressor mediators (IL-10 and programmed death-ligand 1).[5] Previous findings in SARS, H5N1 influenza, and pandemic H1N1 influenza already described a close connection between viral load, hypercytokinaemia, and disease severity. Consequently, hypercytokinaemia would be an additional clue supporting that severe COVID-19 patients have difficulties in controlling SARS-CoV-2 replication.

Focusing exclusively on inflammation as a major driver of severe COVID-19 could lead to misconceptions that affect the design of therapeutic interventions. Anti-inflammatory drugs do not work for all patients with severe disease. For patients on ventilators, dexamethasone reduces mortality by about a third, and for patients requiring only oxygen, mortality is cut by about a fifth. Drugs that decrease viral replication could mediate complementary effect to those that modulate inflammation, because they could help to ameliorate pathogenic events potentially linked to a direct viral action, such as endothelitis[10] and its associated prothrombotic events. Moreover, by decreasing viral replication, antivirals could indirectly help to control hyperinflammation and its associated deleterious events.

Monitoring plasma viral load or the presence of antigenaemia could represent a useful tool for early identification of patients at risk of deterioration. Quantification of viral load in respiratory samples has technical limitations (sample volume and heterogeneous composition), whereas plasma could represent a better option for monitoring viral load in patients with COVID-19 (fixed volume and more homogeneous composition). A pandemic is an opportunity to learn. We must build models on the evidence as it emerges and continue to change those pieces that do not explain all of the data. Models based on reductionist approaches lead to incorrect solutions. This is a viral disease, not an autoimmune one. In conclusion, the available evidence would support combined strategies to simultaneously control viral replication and deleterious inflammation, based on specific indicators or biomarkers of both pathophysiological processes. Effective antiviral treatments are nonetheless needed to achieve this goal.

See Online for appendix

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