

Anticoagulants and Immunosuppressants in COVID-19: Bullets to Defeat MicroCLOTS

Since the first cases of a different type of pneumonia in Wuhan, China in December 2019, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected more than 6.3 million people, with 376,294 confirmed deaths in 185 different countries as of June 1, 2020.^[1]

As other viruses from the Coronaviridae family, SARS-CoV-2 infection entails a systemic syndrome (COVID-19) in which respiratory symptoms represent a hallmark. The disease has a benign course in the majority of patients, with little to no symptoms. However, a quarter requires hospital admission,^[2] while one in ten needs intensive care.^[3] Therefore, considering the high number of infected (due to the elevated level of transmissibility, also by asymptomatic people), the pandemic outbreak of COVID-19 determined an extremely high number of hospital admissions, with increasing levels of stress on the different national health systems.

Hospitals were required to create new wards or modify preexisting wards to accept COVID-19 patients,^[4] to develop separated clinical pathways and to overcome the shortage of devices and personnel (number of noninvasive ventilators, oxygen supplementation, reorganization of medical staff) rapidly. The need to continue to treat different emergencies and serious oncological patients, preserving criteria of efficiency and safety, was a further important challenging imperative. The increasing clinical experience and scientific research are providing continuous findings to better characterize the severe acute respiratory distress syndrome (ARDS), associated with COVID-19, which resulted in different from the typical ARDS we were used to.^[5] Furthermore, increasing clinical evidence, laboratory findings, and autopsy reports indicate how COVID-19 can cause multiorgan damage,^[6,7] related to a vascular endothelium dysfunction resulting from microvascular thrombosis and immune dysregulation.

Based on our clinical experience after treating more than 1000 COVID-19 patients with ARDS, we suggested the use of the term MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) to describe the atypical pulmonary involvement in COVID-19.^[8]

We hypothesized that SARS-CoV-2 can trigger a massive host response in some patients, through different mechanisms such as the activation of alveolar macrophages and the complement cascade. The resultant massive release of proinflammatory cytokines as interleukin (IL)-1, IL-6, IL-8, and interferon- γ contributes

to determining a severe tissue injury, vascular endothelial and alveolar epithelial cell damage, and microvascular thrombosis. These mechanisms could explain the early clinical features of patients with severe COVID-19, showing ventilation/perfusion imbalances, loss of hypoxic vasoconstriction reflexes, lactate dehydrogenase, and D-dimer elevations.^[8]

Furthermore, the cellular damage and inflammatory response could be elicited by an interaction between the virus and the cell surface receptor angiotensin-converting enzyme 2 (ACE-2), expressed on the surface of lung epithelial cells, enterocytes of the small intestine, arterial, and venous endothelial cells, and in arterial smooth muscle cells of multiple organs. This mechanism could be involved in damages to other vital organs, including the kidneys and the brain in the later stage of the disease.^[6,7] The profound systemic inflammatory response seems to be responsible for COVID-19-associated coagulopathy rather than the virus itself. In fact, as an increasing number of reports confirm that severe COVID-19 implies an elevated rate of life-threatening thrombotic complications, a close monitoring of D-dimer, fibrinogen, prothrombin time, partial thromboplastin time, and platelet count should be performed.^[9] While the role of antifibrinolytic drugs is still under investigation,^[10] current literature agrees that all COVID-19 patients receive systemic anticoagulation. The role of prophylactic versus therapeutic dose anticoagulation is still a subject of debate in the scientific community.^[11]

Future guidelines for COVID-19 will recognize the key role of early heparin in SARS-CoV-2, including the possibility to start anticoagulants at home. It is possible that early anticoagulation may contribute to avoiding the worsening of the disease, resulting in a reduction of the burden of excessive hospital admissions on healthcare systems.

Even more importantly, since these MicroCLOTS have an immunological etiopathology, probably relies on immunosuppressive drugs or on those preventing or interrupting the cytokines storm. In our hospital, we had beneficial results with the use of high dose intravenous anakinra, a cheap interleukin 1 blockade^[12] and tocilizumab^[13] in patients with ARDS managed outside the intensive care unit. We also had promising findings with complement C3 inhibitor^[14] and reparixin.^[15]

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