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.

CHEST

Defibrotide Has a Role in COVID-19 Therapy

Antonio Macciò, MD
Giorgio La Nasa, MD
Sara Oppi, MD
Clelia Madeddu, MD
Cagliari, Italy

Infection with SARS-CoV-2 caused the emergence of COVID-19. COVID-19 presents as an immune-mediated inflammatory disease, in which a crucial role is played by macrophages.

COVID-19 is divided into different stages of severity and is characterized by specific symptoms and distinct alterations of hematologic and blood chemistry parameters.[1] These symptoms highlight the evolution of a worsening inflammatory response with specific changes in the neutrophil-to-lymphocyte ratio, elevated levels of acute-phase proteins (C-reactive protein, fibrinogen, and ferritin), high values of proinflammatory cytokines, in particular, IL-6, and above all, the appearance of specific indicators of progressive thrombotic phenomena.[2] These changes are consistent with the different stages of the immune response against pathogens, specifically, the resistance and tolerance phases. Notably, proinflammatory cytokines in the tolerance phase aggravate the damage induced by immunopathology and associated necrosis and are responsible for the most severe symptoms.[3]

Thrombotic complications are among the most critical issues in patients with COVID-19 and may induce severe disseminated intravascular coagulation and pulmonary intravascular coagulation.

FOR RELATED ARTICLE, SEE PAGE 346

AFFILIATIONS: From the Department of Gynecologic Oncology (A. M.), Azienda di Rilievo Nazionale ed Alta Specializzazione (ARNAS) G. Brotzu, and the Department of Surgical Sciences, University of Cagliari; the Department of Medical Sciences and Public Health (G. L., C. M.), University of Cagliari; and the Hematology and Transplant Center (G. L., S. O.), Businco Hospital, ARNAS G. Brotzu.

CORRESPONDENCE TO: Antonio Macciò, MD; email: antoniomaccio56@gmail.com

DOI: https://doi.org/10.1016/j.chest.2022.04.143

SARS-CoV-2 attaches to the cell receptor angiotensin-converting enzyme 2, primarily expressed in type 2 alveolar cells, and gains entry into cells in the lung, which is the primary site of infection. The thrombotic phenomena originate in the same way as the disease: the aggressive damage to the endothelium and the specific activation of macrophages and their associated destruction lead to the activation of the platelet aggregation cascade. In fact, SARS-CoV-2 directly infects alveolar macrophages, which are important in inducing thrombotic events.[4] Infected alveolar macrophages activated by the virus during the early stages of COVID-19 induce the production of proinflammatory cytokines, mainly IL-6, and reactive oxygen species (ROS), contributing to endothelial tissue damage and dysfunction. In addition, activated macrophages secrete the procoagulant prothrombinase, which mediates the establishment of fibrin deposition.[5] Macrophages also stimulate fibrinogen and thromboplastin synthesis in the liver. Endothelial cells are damaged by cytokines and ROS, resulting in exposure of subendothelial matrix elements, especially collagen and tissue factor (TF), which in turn trigger platelet activation and TF-mediated production of thrombin and fibrin. Moreover, endothelial injury is accompanied by damage to the "glycocalyx." This activates the synthesis of adhesion proteins, which mobilize platelets and leukocytes into the endothelium.[6] ROS originating from macrophages disable endothelium-derived nitric oxide, mediate cell signaling, and foster protein alterations, contributing to the start and evolution of endothelial injury. Besides ROS, proinflammatory cytokines stimulate the nuclear factor (NF)-κB pathway, which activates the apoptosis of endothelial cells by initiating mitochondrial injury and endoplasmic reticulum stress.[7] A further mediator associated with inflammatory responses, macrophage-stimulating factor 1, primarily triggers endothelial cell apoptosis by activating mitochondrion-dependent cell death by inhibiting mitophagy.[8] Thus, changes in the vascular endothelium cause increased thrombin production both systemically and in the lungs, leading to fibrin deposition with subsequent coagulopathy. Another determinant is hypoxia-inducible factor, which appears during the tolerance phase; it drives the macrophage polarization into M1 cells, the main

producers of IL-6 and ROS. Moreover, hypoxia-inducible factor enhances the NF-κB pathway-induced inflammation response that, in succession, increases complement-mediated endothelium injury.[9]

Notably, these phenomena mediated by macrophages also likely occur after vaccine administration, contributing to some of the side effects of thromboembolism reported in the literature.[10]

Exact knowledge of the pathogenic events and the evolution of COVID-19 into different stages is crucial to elucidate the specific mechanisms involved in thrombotic complications and to investigate the most appropriate treatment in each case.

In this regard, an interesting article published in this issue of *CHEST*, by Frame et al,[11] investigates the safety of a profibrinolytic drug, defibrotide, in an open-label prospective clinical trial involving a population of patients with severe COVID-19 and related ARDS. Defibrotide works via multiple mechanisms of action, specifically targeting several pathways involved in the pathogenesis of thrombotic phenomena in COVID-19, as discussed by Frame et al[11] in their article. Indeed, other authors have indicated that defibrotide, besides its profibrinolytic activity, can exert antithrombotic effects through other mechanisms involving antiinflammatory and antioxidant pathways.[4] Defibrotide hinders the synthesis of proinflammatory cytokines, such as IL-6, by activated macrophages and mononuclear cells; inhibits ROS generation by activated monocytes/macrophages; and can restore nitric oxide generation under conditions of oxidative stress. Furthermore, in vitro and ex vivo work showed that defibrotide inhibits the TF expression stimulated by inflammatory molecules, raises the synthesis of thrombomodulin in endothelial cells, downregulates prothrombinase action, decreases thrombin-mediated platelet aggregation, and increases platelet- and leukocyte-endothelial cell interactions. Defibrotide is also able to reduce the activity of heparanase, which is a key mediator of macrophage activation and polarization.

Frame et al[11] demonstrate that the use of defibrotide is safe and well tolerated by patients with COVID-19. Remarkably, the authors also achieve positive and promising results in terms of improvement of the main laboratory parameters, such as D-dimer; clinical parameters; respiratory function; and discontinuation of oxygen support. Therefore, the Frame et al[11] study represents an encouraging basis for adding defibrotide to the therapeutic "armamentarium" against COVID-19-associated coagulopathy. Because the profibrinolytic, inflammatory, and antioxidant activities of defibrotide are able to restore and preserve endothelial function, understanding when to start defibrotide administration is essential.[12]

It may be presumed that defibrotide can crucially treat the initial phases of COVID-19, when induction of endothelial damage by the increased expression of procoagulant factors, and the stimulation of platelet aggregation, mainly occur. Conversely, low-molecular-weight heparins are assumed to have a role when perturbations in the inflammatory mediators, such as an increase in IL-6 and fibrinogen and its degradation products, are most apparent. In this regard, we would like to highlight that precise timing is required for the use of these drugs at a prophylactic dose and for adjusting their therapeutic dose in the later phases of COVID-19, in association with other drugs such as antithrombin III.[12]

Therefore, defibrotide could be used in the initial stages of COVID-19 before administering, or replacing defibrotide with, low-molecular-weight heparin; this may result in better outcomes and prognosis for these patients.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

References

1. Cordon-Cardo C, Pujadas E, Wajnberg A, et al. COVID-19: staging of a new disease. *Cancer Cell*. 2020;38(5):594-597.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in *Lancet* 2020;395(10229):1038]. *Lancet*. 2020;395(10229):1054-1062.
3. Macciò A, Oppi S, Madeddu C. COVID-19 and cytokine storm syndrome: can what we know about interleukin-6 in ovarian cancer be applied? *J Ovarian Res*. 2021;14(1):28.
4. Macciò A, Madeddu C, Caocci G, La Nasa G. Multifactorial pathogenesis of COVID-19-related coagulopathy: can defibrotide have a role in the early phases of coagulation disorders? *J Thromb Haemost*. 2020;18(11):3106-3108.
5. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol*. 2020;20(6):355-362.
6. Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. *J Thromb Haemost*. 2018;16(2):231-241.
7. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. *Vascul Pharmacol*. 2018;100:1-19.
8. Lu K, Zhao J, Liu W. Macrophage stimulating 1-induced inflammation response promotes aortic aneurysm formation through

triggering endothelial cells death and activating the NF-κB signaling pathway. *J Recept Signal Transduct Res*. 2020;40(4):374-382.

9. Marchetti M. COVID-19-driven endothelial damage: complement, HIF-1, and ABL2 are potential pathways of damage and targets for cure. *Ann Hematol*. 2020;99(8):1701-1707.
10. Maccio A, Madeddu C. Potential role of macrophage activation in mediating thrombotic complications associated with the different vaccines against COVID-19. *Eur Rev Med Pharmacol Sci*. 2021;25(20):6176-6178.
11. Frame D, Scappaticci GB, Braun TM, et al. Defibrotide therapy for SARS-CoV-2 ARDS. *Chest*. 2022;162(2):346-355.
12. Macciò A, Madeddu C, Caocci G, Oppi S, La Nasa G. Defibrotide in the COVID-19 coagulopathy: what is the timing? *J Thromb Haemost*. 2020;18(11):3113-3115.