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Defibrotide in the COVID-19 coagulopathy: What is the timing?

Dear Editor,

We appreciate the insightful comments by Richardson et al[1] about our letter,[2] which contributed to better explore the fundamental concepts of our study by providing important, additional information for reflection.

The identification of additional mechanisms involved in the endothelial damage as that described by Richardson et al[1] mediated by the p38 MAPK pathway, which is upregulated as a result of the binding of SARSCoV2 on ACE2 receptors on the surface of endothelial cells and, in turn, activates the transcription of the proinflammatory cytokines, poses an important problem regarding the timing of the onset of coagulopathy in patients with COVID-19. Consequently it is fundamental to understand the timing of the start of anticoagulant therapy based on the drugs available to date[3] to establish a targeted etiopathogenesis approach (ie, based on the etiopathogenesis mechanisms).

The subdivision of COVID-19 into different stages (paucisymptomatic, mild, and critically severe) would reinforce this exigency, and strongly requires us to understand when the coagulopathy begins. Therefore, it is essential to pay attention to the specific phases of the defense mechanism of our body against the pathogen in order to improve our understanding of what happens during the course of COVID-19. SARSCoV2 infection, as previously described, involves

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not only the endothelial cells present mainly in the lungs, but also the endothelial cells present in other organs, including the kidney, heart, small intestine, and liver;[4] macrophages associated with the endothelium; and all cells that express the ACE2 receptor, which is known to be the key factor favoring the entry of SARSCoV2 into the cells.[4]

It is well known that following viral infection, mechanisms typical of the resistance phase of the immune response are activated.[5] During this phase, the specific cell-mediated immune response exerts its cytotoxic effect, to which it is possible to attribute the initial phenomena that triggers the coagulopathy. Indeed, during the first phase of resistance, the immune system recognizes the pathogen by antigens and attempts to eliminate it; the activity of macrophages, dendritic cells, natural killer cells, T and B lymphocytes, and in some cases neutrophils, is a determinant of the effectiveness of the immune response. Additionally, the activated lymphocytes (ie, CD8 + cells) can directly disrupt the infected cells inducing tissue injury. Furthermore, the activation of the complement cascade by the interaction between the antibodies and the infected cells further promotes the inflammatory reaction, thereby contributing to the endothelial damage.[6] Moreover, as widely described in our previous letter, infected macrophages seem to produce other prothrombotic factors such as prothrombinase.[7] Once activated, these immune cells also release a range of molecules that can induce tissue damage, including interferons, cytokines, cationic proteins, lipid mediators, metalloproteinases, and reactive oxygen species (ROS). ROS in particular strongly contributes to the tissue damage and endothelial dysfunction, thus favoring the activation of pathogenesis of thrombosis.[8] Alterations in the vascular endothelium thus results in increasing generation of thrombin, both systemically and locally, in the lungs of patients with severe pneumonia, leading to the deposition of fibrin with subsequent tissue damage and coagulopathy.[9]

The upregulation of procoagulant factors in the first phase of resistance seems to aggravate the next phenomenon of disseminated coagulation at multiple levels. The factors typical of the tolerance phase are, however, determinants for these following events. Undoubtedly, the necrosis associated with the immunopathology plays, in the most advanced phases of the disease, an even more crucial role that actually influences the patient prognosis. This is well demonstrated by the established association between the increased levels of fibrinogen, C-reactive protein, interleukin 6 (IL-6), ferritin, D dimer, and mortality in patients with COVID-19.[10] Hypoxia-inducible factor (HIF) plays a determinant role in this second phase (the tolerance phase). HIF-1 can serve as a critical transcriptional regulator of the adaptive immunity and the inflammation during COVID-19 infection. HIF-1 signaling during the activation of certain immune cells, most notably macrophages, as well as endothelial cells, induces a cellular metabolic switch by promoting aerobic glycolysis, allowing the cells to respond appropriately to the dramatic changes in energy requirements that occur upon their activation and in adapting to the hypoxic conditions that can prevail in inflamed and necrotic tissues. Of note, the metabolic shift mediated by the HIF-1 in macrophages drives their polarization into the M1 phenotype, which mainly produces IL-6 and ROS, the key molecules involved in the immunopathology and related thrombotic disorders.[11] Additionally, HIF-1 expression enhances in the alveolar lung epithelial cells the nuclear factor kappa-light-chain enhancer of activated B cells pathway-mediated inflammatory response, which in turn augments the complement-mediated endothelial damage.[6]

Therefore, we believe that the rationale for the use of defibrotide as a drug for preventing thrombosis, owing to its anti-inflammatory and antioxidant properties,[12] should be corroborated by the information on its appropriate time of use. It is intuitively assumed that defibrotide can play an important role during the resistance phase, when the first phenomenon of activation through the increasing expression of the procoagulant factors and activation of platelet aggregation is the central event. However, drugs such as low molecular weight heparin or similar molecules are expected to play a role when changes in the inflammation parameters such as high levels of IL-6 and increased levels of fibrinogen and its degradation products are most evident.[10] In this regard, it should be clearly stated that there is a specific time for these drugs to be used at a prophylactic dosage in order to accommodate their therapeutic dosage in the later phases of COVID-19. Therefore, it is in this population of patients candidates for low molecular weight heparin treatment that an important aspect, which has been little described to date, should be considered, ie, the dosage of the serum values of antithrombin III, and the introduction of antithrombin III into therapy protocols when its levels are not adequate.

In this context, the results of the ongoing DEFACOVID phase IIb randomized trials (clinicaltrials.gov:NCT04348383), could provide interesting and useful data.

KEYWORDS

coagulopathy, COVID-19, defibrotide, resistance, tolerance

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CONFLICTS OF INTEREST

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

AM, CM, SO, GC, and GLN contributed to study design, data analysis, literature review, manuscript drafting, and final editing.

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Reply to "Is Anticoagulation Reversal Needed/Warranted with Latest Data?"

Dear Editor,

It is with great interest that I recently watched the web-based ISTH educational program "Is Anticoagulation Reversal Needed/Warranted with Latest Data?" and the following is a reply to the participants, Dr. Hunt, Dr. Connors, and Dr. Weitz.[1]

1. Dr. Weitz, during this video you say about andexanet alfa (a.k.a. coagulation factor Xa (recombinant), inactivated-zhzo) that "the data supporting its use are there, through the Annexa-4 study, and the issue with it is the cost. It's expensive."

We should clarify that cost is just one of several issues. Instead, the most frustrating aspect of Annexa-4 is that it did not help us to address the important issue of real world comparison. In other words, "How does this new medicine compare to what hospitals are already doing?"

Annexa-4 shows approximately 80% hemostatic efficacy for the patients who were enrolled into this study. Therefore, andexanet alfa does have some effect, but we can only speculate about a comparison with prothrombin complex concentrates (PCCs). Both strategies appear to have some merit. It is possible that andexanet alfa is better than PCCs, but maybe not. Also, if it is better, we don't know how much better it could be.

2. Dr. Weitz, you then make a comment about a recent meta-analysis that comes to "the conclusion that four factor PCC has similar efficacy as andexanet alfa." This was the conclusion from a recent abstract that appeared at the ISTH 2020 Congress.[2] Dr. Connors, in relation to this, you comment, "It is very hard in the real world to match the selection criteria and eligibility criteria that the Annexa-4 trial had, with regard to ICH size and to when the last dose of drug was ingested. A little bit hard sometimes for the emergency room staff to discern all of that. And so I would say that some of the real world data that suggest that andexanet does not hold up as well is simply because the patient populations are different."

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