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

Fibrinolytics as an ARDS Salvage Option

Promising, But ARDS Prevention Options Are Needed Urgently

COL Andrew P. Cap, MD, PhD (Army)
Fort Sam Houston, TX

Since the earliest days of the COVID-19 pandemic, hypercoagulability has been recognized as a driver of morbidity and death in patients with severe SARS-CoV-2 infections.[1] Indeed, the concept of thromboinflammation has gained currency as an overarching pathophysiologic mechanism that drives multiorgan failure in this disease. Widespread microvascular and large vessel thrombosis in COVID-19 appears to be caused by a combination of direct viral infection via the angiotensin-converting enzyme 2 receptor, and consequent injury of endothelial cells, as well as by activation of endothelial cells by cytokines, and by the growth factor, angiopoietin-2, among others.[1,2] These stimuli cause the expression of tissue factor, adhesion molecules that include intercellular adhesion molecule and Von Willebrand factor, and downregulation of protective, anticoagulant pathways like thrombomodulin, endothelial protein C receptor, and TEK tyrosine kinase, endothelial (TIE2).[3-5] The net effect is an endotheliopathy that creates a prothrombotic state, similar to that observed in bacterial sepsis, trauma, and other systemic inflammatory states.[6]

Early recognition of the loss of coagulation homeostasis prompted clinical interest in the optimization of anticoagulation strategies in the management of COVID-19. Recently published studies suggest that early use of therapeutic anticoagulation, prior to the onset of critical illness, may improve outcomes.[7] By contrast, therapeutic anticoagulation in critically ill patients with COVID -19 was not superior to standard thromboprophylaxis.[8] Taken together, these studies suggest that early interventions to abrogate thrombosis, coupled with antiinflammatory treatments like corticosteroids, reduce the severity of SARS-CoV-2 infection and can prevent respiratory failure, multiorgan failure and death. Unfortunately, this approach is not always successful, and some patients present too late or with rapidly progressive disease. What salvage options are available?

FOR RELATED ARTICLE, SEE PAGE 710

AFFILIATIONS: From the US Army Medical Corps, US Army Institute of Surgical Research.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

DISCLAIMER: The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

CORRESPONDENCE TO: COL Andrew P. Cap, MD, PhD (Army); email: andrew.p.cap.mil@mail.mil

DOI: https://doi.org/10.1016/j.chest.2021.11.022

It is with these patients in mind that the authors conducted an adaptive design, open-label randomized controlled trial of tissue plasminogen activator (tPA) in combination with heparin to treat respiratory failure in COVID-19.[9] The hypothesis informing the trial was that inducing fibrinolysis with tPA, in combination with therapeutic anticoagulation, would improve oxygenation compared with standard of care in ARDS. As cited by Barrett et al[10] in their rationale for the current trial, the feasibility of using fibrionlytics to treat ARDS caused by a variety of causes was explored by Hardaway et al[11] in a seminal study published 20 years ago.

The authors are to be commended for their timely execution of a sophisticated multicenter trial during extremely difficult pandemic circumstances, in the midst of constantly changing clinical practice and evolving severity of disease. This pilot-scale study demonstrated the feasibility of treating COVID-induced ARDS with thrombolytics. The primary endpoint was PaO_2/FIO_2 improvement from before to after intervention at 48 h after randomization. The adaptive design of the trial facilitated identification of a tPA bolus followed by full therapeutic anticoagulation with unfractionated heparin (UFH) infusion as a superior regimen to tPA bolus followed by a tPA infusion over 24 h combined with low-dose UFH and followed by a no-bolus titration of UFH to an activated partial thromboplastin clotting time of 60 to 80 seconds. The latter regimen showed no improvement in PaO_2/FIO_2 compared with control subjects, likely because of

inadequate anticoagulation after thrombolysis, resulting in re-thrombosis. By contrast, the tPA bolus followed by full anticoagulation demonstrated significant and sustained improvements in Pao_2/Fio_2 and suggests that clinically relevant endpoints such as ventilator free days and mortality rates could also be improved. Importantly, there were no bleeding adverse events in either intervention group. This is probably due to careful patient selection with a requirement for a nonfocal neurologic examination or brain imaging without evidence of stroke within 4.5 h of starting tPA.

These promising results justify a larger, phase III study. There are, however, many areas of uncertainty: 85% of patients who were screened for this study were ineligible. This raises the question of whether a phase III study is even feasible. A deeper exploration of patient selection and potential relaxation of eligibility criteria (given the safety signal in this pilot study) would be helpful in justifying and increasing the enthusiasm for a phase III study. Perhaps assessment of bleeding risk could include measurements of fibrinogen, platelet count, viscoelastic clotting studies, or other biomarkers like plasminogen activator inhibitor 1. Also, the timing of intervention must balance the role of thrombolysis as a salvage regimen with the likelihood that delayed treatment, after tissue has been thrombosed for some time, may be ineffective. The authors included patients with a Pao_2/Fio_2 ratio of < 150 for > 4 h in duration. Perhaps relaxation of these parameters is possible, or other factors such as imaging studies (eg, evidence of pulmonary embolism) could inform treatment timing.

An innovative approach to ARDS management that expands the armamentarium is attractive. It should be noted, however, that massive activation of plasmin through tPA administration not only increases bleeding risk but is likely to have off-target effects on the immune response to COVID-19. The pleomorphic effects of plasmin on the immune system are becoming better appreciated, but pharmacologic manipulation of plasmin activity in ARDS and COVID-19, in particular, should be studied carefully.[12] Finally, while a clinical salvage option like tPA, whether delivered systemically or catheter-directed, would certainly be useful, options for preventing evolution of COVID-19 and other pulmonary infections to ARDS are urgently needed. Targeting pathways that reduce endothelial activation and loss of microvascular homeostasis, for example by inhibiting angiopoietin-2/TIE2 signaling or by modulating thrombin production through the protein C pathway, could reduce the burden of microvascular thrombosis and the need for salvage fibrinolysis coupled with therapeutic anticoagulation.[1,5]

References

1. Gando S, Wada T. Thromboplasminflammation in COVID-19 coagulopathy: three viewpoints for diagnostic and therapeutic strategies. *Front Immunol*. 2021;12:649122.
2. Nagashima S, Mendes MC, Martins APC, et al. Endothelial dysfunction and thrombosis in patients with COVID-19: brief report. *Arterioscler Thromb Vasc Biol*. 2020;40(10):2404-2407.
3. Francischetti IMB, Toomer K, Zhang Y, et al. Upregulation of pulmonary tissue factor, loss of thrombomodulin and immunothrombosis in SARS-CoV-2 infection. *EClinicalMedicine*. 2021;39:101069.
4. Birnhuber A, Fließer E, Gorkiewicz G, et al. Between inflammation and thrombosis: endothelial cells in COVID-19. *Eur Respir J*. 2021;58(3):2100377.
5. Schmaier AA, Hurtado GMP, Manickas-Hill ZJ, et al. Tie2 activation protects against prothrombotic endothelial dysfunction in COVID-19. *JCI Insight*. 2021;6(20):e151527.
6. Ito T, Kakuuchi M, Maruyama I. Endotheliopathy in septic conditions: mechanistic insight into intravascular coagulation. *Crit Care*. 2021;25(1):95.
7. ATTACC Investigators, ACTIV-4A Investigators, REMAP-CAP Investigators, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. *N Engl J Med*. 2021;385(9):790-802.
8. REMAP-CAP Investigators, ACTIV-4A Investigators, ATTACC Investigators, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med*. 2021;385(9):777-789.
9. Barrett CD, Moore HB, Moore EE, et al. Study of alteplase for respiratory failure in SARS-CoV-2 COVID-19: a vanguard multicenter, rapidly adaptive, pragmatic, randomized controlled trial. *Chest*. 2022;161(3):710-727.
10. Barrett CD, Moore HB, Moore EE, et al. Fibrinolytic therapy for refractory COVID-19 acute respiratory distress syndrome: xcientific rationale and review. *Res Pract Thromb Haemost*. 2020;4(4):524-531.
11. Hardaway RM, Harke H, Tyroch AH, Williams CH, Vazquez Y, Krause GF. Treatment of severe acute respiratory distress syndrome: a final report on a phase I study. *Am Surg*. 2001;67(4):377-382.
12. Medcalf RL, Keragala CB. Fibrinolysis: a primordial system linked to the immune response. *Int J Mol Sci*. 2021;22(7):3406.