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Fibrinolytic or anti-plasmin (nafamostat) therapy for COVID-19: A timing challenge for clinicians

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To the Editor

This is a correspondence to the letters entitled "An Ounce of Prevention may Prevent Hospitalization" [1], "Consideration of Tranexamic Acid Administration to COVID-19 Patients" [2], and "Anti-Protease Treatments Targeting Plasmin (ogen) and Neutrophil Elastase may be Beneficial in Fighting COVID-19" [3]. Since the publication of our review [4], multiple studies have reported clinical management of COVID-19 infection with plasmin modulators: nafamostat, a broad spectrum antiprotease that has inhibitory effects on plasmin activity, and alteplase (tPA), a plasmin activator. Interestingly, while both of these therapies may be useful, their mechanisms of action are in contrast. Therefore, the dilemma for physicians in deciding which therapy to use will be the phase of COVID-19 infection [5]. Herein, we briefly summarize the current progress of these two opposing plasmin-related therapies.

The dynamics of COVID-19 are composed of pre-infected (healthy), pre-symptomatic, and symptomatic stages [6]. It is believed that early in COVID-19 infection, patients are not yet hypercoagulable, and inhibition of plasmin formation, or inhibition of plasmin activity itself, may be beneficial to slow viral activity until adaptive immunity can overwhelm the virus [4]. During the later stages of COVID-19, patients are hypercoagulable and are prone to form clots in a variety of end-organs, including the lung, that limits perfusion, and therefore, oxygenation of blood [6]. Patients that are early within the infection window and have co-morbidities that increase plasmin (ogen), including, but not limited to, diabetes, hypertension, renal insufficiency, and cardiovascular disease, may benefit from anti-plasmin therapy, such as nafamostat. Furthermore, one of the benefits of drugs such as nafamostat (or camostat) is that in addition to inhibiting plasmin activity (anti--SARS-CoV-2), they are serine proteases that can act as anti-coagulants for disseminated intravascular coagulation (DIC) [7–9]. This is important because one concern with anti-fibrinolytic therapy with tranexamic acid is preventing clot dissolution of existing and/or newly formed clots.

A case series of three patients treated with nafamostat combined with favipiravir in a non-intensive care unit (ICU) elderly patients led to recovery and discharge for these patients [10]. Two other studies reported the effects of nafamostat and camostat for 12 ICU patients [11, 12]. Of these, ten patients recovered towards rehabilitation, one patient died, and one remained in ICU. Nafamostat was discontinued due to hemothorax and hyperkalemia in one case when combined with heparin [12]. Hyperkalemia may be the major adverse event of nafamostat-treated COVID-19 patients [13]. These case series are not randomized controlled trials (RCT). However, phase 2 and 3 RCT trials have been registered to test the safety and efficacy of these anti-plasmin medications, 6 using nafamostat and 14 using camostat in both outpatient and inpatient settings. Of note, other plasmin inhibitors being tested are aprotinin (NCT04527133), inhaled α1-antitrypsin (NCT04385836), tranexamic acid (NCT04338074), and doxycycline (NCT04371952).

Hypercoagulation and hyperinflammation are common in patients in the later stages of COVID-19 infection, particularly those in the ICU. The massive hypercoagulable state in COVID-19 is generally systemic, while hyperfibrinolysis is limited to the inflamed pulmonary capillaries. This is supported by "fibrinolysis resistance" or "fibrinolysis shutdown" in whole blood clot lysis *in vitro* [14–16]. It is also possible that circulating PAI-1, but not anti-plasmin, may be robust in COVID-19 [17]. The coexistence of elevated D-dimers and hypercoagulable state reveals uncoordinated fibrinolysis and thrombosis, leading to DIC. We recently described the beneficial effects of instilled uPA in a murine model of aspiration-induced ARDS [18]. Furthermore, a meta-analysis has indicated that fibrinolytic therapy can improve ARDS [19]. Most of the patients had received prophylactic or intensified anticoagulation before alteplase (tPA) administration. Thus, anticoagulation therapy may not be a substitute for fibrinolytic therapy.

Again, case series have reported treating COVID-19 patients with tPA for ARDS, acute ischemic stroke (AIS), PE and massive thrombosis, and ST-elevation myocardial infarction (STEMI) [20–30]. There are two types of patients: 1) mild cases without severe pulmonary illness but

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single thrombus, AIS, and/or STEMI and 2) critically ill patients with severe pulmonary dysfunction and massive thromboembolism. For some of these patients, catheter-directed delivery of tPA could be used to resolve the local thrombus in the AIS, STEMI, and patients with PE and DVT with fewer side-effects. However, in critically ill patients with severe pulmonary dysfunction and systemic thromboembolism, tPA may be useful to lessen the overall clot burden and improved perfusion to critical organs, including the lung. Low doses of tPA (25 mg/2h + 25 mg/22h) followed by heparin have been applied in early trials with improved P/F ratio, increased D-dimer, and reduced fibrinogen level [20,23,25]. In some cases, a higher "salvage" dose (50 mg/2h + 50 mg/22h) was tested [21,26] and some trials have used dosing typical for acute pulmonary embolism or AIS (100 mg/2h) [22,24]. A recent case series adapted two strategies (10 mg bolus + 90 mg/90min or 50 mg/90min) [27]. The outcomes were poor when tPA was used as salvage therapy [24,26,29], and patients treated with a 100 mg bolus showed a high discharged rate from ICU [22,30]. Hemorrhage, a major concern of fibrinolytic therapy, was rarely described by these studies.

In addition to intravenous routes of fibrinolytic therapy, nebulized forms of streptokinase improved oxygenation better than nebulized heparin in the treatment of ARDS and reduced in-hospital mortality [31]. Similarly, the benefits were documented in ARDS patients resistant to conventional interventions [32]. The beneficial effects of nebulized plasminogen activators (uPA and tPA) have not been reported in COVID-19. An interventional phase 2 trial is recruiting patients for nebulized tPA (NCT04356833). It is proposed that inhaled fibrinolytics may have the least systemic side-effects and alleviate pulmonary injury to the utmost for non-ICU patients with pneumonia only. Special attention shall be paid to the different responses to fibrinolytic therapy among injured organs. This is particularly worthy of treating COVID-19 patients with multiple organ failure. For example, the plasmin system upregulates renal epithelial sodium channels (ENaC), which may worsen pre-existing hypertension or cause an increase in blood pressure [33,34]. In contrast, ENaC activation by plasmin activators alleviates pulmonary edema by improving alveolar fluid clearance [18,35–38].

In conclusion, we propose that the use of anti-plasmin or plasmin-activating therapies depends on the timing of COVID-19 infection, and this timing is a dilemma for physicians. The aforementioned case studies for both therapies suggest these therapies may be beneficial to patients infected with COVID-19. Nafamostat and camostat would theoretically be used as prophylaxis and pre-emptive therapy during the early phase of infection, while tPA would mostly be used for rescue therapy for the later stages of infection. RCTs are planned and are recruiting patients to test these hypotheses and will hopefully provide evidence for the timing, dose, route, and monitoring strategy for these plasmin modulators. The effectiveness of nafamostat and tPA cannot be compared directly due to differences in the timing of potential clinical efficacy and mechanism of action.

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Contributors

HLJ, TJN, and BMW were responsible for searching the literature and preparing the manuscript.

Declaration of competing interest

None of the authors have any conflict of interest to declare.

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Hong-Long Ji*
Department of Cellular and Molecular Biology, University of Texas Health Science Centre at Tyler, Tyler, TX 75708, USA
Texas Lung Injury Institute, The University of Texas Health Science Centre at Tyler, Tyler, TX 75708, USA

Brant M. Wagener
Division of Molecular and Translational Biomedicine, USA
Division of Critical Care Medicine, Department of Anesthesiology and Perioperative Medicine, University of Alabama at Birmingham, Birmingham, AL, USA
E-mail address: bwagener@uabmc.edu.

Timothy J. Ness
Division of Molecular and Translational Biomedicine, USA
E-mail address: tness@uabmc.edu.

Runzhen Zhao
Department of Cellular and Molecular Biology, University of Texas Health Science Centre at Tyler, Tyler, TX 75708, USA
E-mail address: Zhao@uthct.edu.

* Corresponding author. Department of Cellular and Molecular Biology, University of Texas Health Science Centre at Tyler, Tyler, TX 75708, USA.
E-mail address: james.ji@uthct.edu (H.-L. Ji).