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# **Is There a Role for Tissue Plasminogen Activator (tPA) as a Novel Treatment for Refractory COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS)?**

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The global pandemic of COVID-19 has begun to oversaturate the world's medical capacity to accommodate a large surge of patients with Acute Respiratory Distress Syndrome (ARDS) (1). ARDS has no effective treatment besides supportive care, with the use of ventilatory strategies encompassing low tidal volumes that limit trans-pulmonary pressures being the mainstay (2). A consistent finding in ARDS is the deposition of fibrin in the airspaces and lung parenchyma, along with fibrin-platelet microthrombi in the pulmonary vasculature, which contribute to the development of progressive respiratory dysfunction and right heart failure (3-5). Similar pathologic findings have now been observed in lung specimens from patients infected with COVID-19 (6). This physiologically destructive activation of the clotting system in ARDS results from enhanced activation and propagation of clot formation together with suppression of fibrinolysis (7-9), and is thought to be mediated by dysfunction of the pulmonary endothelium in the case of Influenza A (10). Targeting the coagulation and fibrinolytic systems to improve the treatment of ARDS has been proposed since at least 2003 (11-14). In particular, the use of plasminogen activators to limit ARDS progression and reduce ARDS-induced death has received strong support from animal models (15-17), and a phase 1 human clinical trial (18). In 2001, Hardaway and colleagues showed that administration of either urokinase or streptokinase to patients with terminal ARDS reduced the expected mortality from 100% to 70% with no adverse bleeding events. Importantly, the majority of patients who ultimately succumbed died from renal or hepatic failure, rather than pulmonary failure.

A recent American Hospital Association assessment indicates that up to 960,000 patients may require mechanical ventilation, for which only 62,000 fully-featured ventilators are currently available, based on a 2009 survey (19). The estimated mortality rate for critically ill

patients infected with COVID-19 is 22- 64%, using statistics from early reports from Hubei Province (18, 20). Taken together, these statistics indicate an emergent need for effective therapeutics to treat and attenuate ARDS secondary to COVID-19 and, particularly to salvage patients who have decompensating respiratory status but no access to a mechanical ventilator or extracorporeal membrane oxygenation (ECMO). We posit that administration of tPA, as a compassionate salvage approach, may have merit in this situation.

Consideration of therapies that are widely available but not recognized for this indication and traditionally considered “high-risk” such as fibrinolytic agents is warranted in this unprecedented public health emergency, since the risk of adverse events from tPA is far outweighed by the certainty of death in patients meeting the eligibility criteria for this treatment. While the prior study by Hardaway et al. evaluating fibrinolytic therapy for treatment of ARDS used urokinase and streptokinase, the more contemporary approach to thrombolytic therapy involves the use of tissue-type plasminogen activator (tPA) due to higher efficacy of clot lysis with comparable bleeding risk to the other fibrinolytic agents. In addition, tPA treatment was reported to have a greater reduction of death, a larger increase in arterial pO<sub>2</sub> and a larger decrease in arterial pCO<sub>2</sub>, compared to untreated controls, than either uPA or plasmin in a comprehensive meta-analysis of animal studies of acute lung injury, although none of those studies included viral-induced ARDS (16).

The dose, route of administration, and duration of treatment remain to be defined, but modeling efforts by individuals interested in this approach are both needed and underway. In animal models of acute lung injury, intra-tracheal and intravenous dosing of fibrinolytic agents

was more effective than nebulized delivery. Based on a large body of experience using tPA for acute treatment of strokes and myocardial infarctions (22, 23), intravenous administration may be the easiest to implement. However, unlike the brief treatment used in those situations where a defined nidus of clot is present without ongoing widespread disruption of the hemostatic system, we believe an initial approach might be to administer 25mg of tPA over 2 hours followed by a 25mg tPA infusion administered over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg. The same exclusion criteria currently in place for stroke and MI treatment could be used, with responders maintained for some period of time on a heparin infusion after completion of the tPA treatment. Exactly which patients would qualify for this salvage treatment similarly remains to be defined, but patients with COVID-19-induced ARDS who have a P/F ratio  $<50$  and a  $pCO_2 > 60$  despite prone positioning and maximal mechanical ventilatory support would seem to be ideal candidates, particularly in settings where ECMO is not a possibility. Furthermore, in scenarios where there is no further mechanical ventilation capacity, this may be appropriate for those with progressive pulmonary deterioration.

Extraordinary times may call for extraordinary measures. If an observational trial of this treatment in the first series of patients is effective and safe, the approach could be readily broadened. This would have multiple patient-related and public health benefits including: 1) earlier weaning from the ventilator to free up more ventilators for other patients in need; 2) preventing patients from progressing to a need for ECMO support, which is likely to be limited in a resource-limited crisis, and 3) leveraging the availability, modest cost, and wide pre-existing clinical familiarity with tPA.

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