Tissue Plasminogen Activator (tPA) Treatment for COVID-19 Associated Acute Respiratory Distress Syndrome (ARDS): A Case Series

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Conflicts of Interest: CDB, HBM, EEM, and MBY have patents pending related to both coagulation/fibrinolysis diagnostics and therapeutic fibrinolytics, and are passive co-founders and holds stock options in Thrombo Therapeutics, Inc. HBM and EEM have received grant support from Haemonetics and Instrumentation Laboratories. MBY has previously received a gift of Alteplase (tPA) from Genentech, and owns stock options as a co-founder of Merrimack Pharmaceuticals. LAV has received grant support from Genentech. JW, NH, RCM, and PKM having nothing to disclose.

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INTRODUCTION

A hallmark of severe COVID-19 is coagulopathy, with 71.4% of patients who die of COVID-19 meeting ISTH criteria for disseminated intravascular coagulation (DIC) while only 0.6% of patients who survive meet these criteria (*1*). Additionally, it has

become clear that this is not a bleeding diathesis but rather a predominantly pro-thrombotic DIC with high venous thromboembolism rates, elevated D-dimer levels, high fibrinogen levels in concert with low anti-thrombin levels, and pulmonary congestion with microvascular thrombosis and occlusion on pathology in addition to mounting experience with high rates of central line thrombosis and vascular occlusive events (e.g. ischemic limbs, strokes, etc.) observed by those who care for critically ill COVID-19 patients (*1-7*). There is evidence in both animals and humans that fibrinolytic therapy in Acute Lung Injury and ARDS improves survival, which also points to fibrin deposition in the pulmonary microvasculature as a contributory cause of ARDS and would be expected to be seen in patients with ARDS and concomitant diagnoses of DIC on their laboratory values such as what is observed in more than 70% of those who die of COVID-19 (*8-10*). The following are 3 case reports of using tissue plasminogen activator (t-PA) in critically ill, mechanically ventilated COVID-19 positive patients with ARDS where extracorporeal membrane oxygenation (ECMO) capabilities, staffing and resources are extremely limited as a result of the current COVID-19 pandemic.

Case 1

75 year-old male with a history of hypertension, hyperlipidemia, type 2 diabetes mellitus, and coronary artery disease presented to the hospital with 1 week of cough, fatigue and fevers. Vital signs on presentation were T 38.5° Celsius, HR 87 bpm, BP 133/78 mm Hg, RR 22, SpO2 91% on room air. CT chest revealed bilateral ground glass opacities with peripheral and basilar predominance; COVID-19 testing was positive. Hydroxychloroquine and azithromycin were started and given for five days. His

oxygen requirement increased from 4 – 6 LPM O2 supplementation on day of admission (DOA) to 100% FiO2 on a non-rebreather mask (NRB) by day 3, with oxygen saturation (SpO2) improving from 85% to 91% with positioning in the awake prone position. Unfortunately, his severe hypoxemia persisted and he was intubated on hospital day (HD) 6 at which time his PaO2/FiO2 (P/F) ratio was 73. His FiO2 requirements remained >60% despite maximal ventilatory strategies, his D-dimer levels were consistently > 50,000 ng/ml for the four days following his intubation and his fibrinogen levels ranged between 375 to 541 mg/dl. On HD 8 his P/F ratio ranged between 140 to 240 and he became anuric for which he was initiated on continuous renal replacement therapy (CRRT); that combined with persistently elevated D-dimer, the decision was made to administer tPA (Alteplase) 25mg intravenously over 2 hours, followed by a 25mg tPA infusion over the subsequent 22 hours. The patient tolerated tPA therapy without bleeding or any other apparent complication. Eleven hours into his tPA infusion his P/F ratio had improved to 408, a 2-fold improvement from pre-tPA. Following completion of the tPA infusion, a heparin infusion was started at 10 units/kg/hour with a PTT goal of 60-80. One hour into his heparin infusion, his P/F ratio worsened to 136. There was a concern for fluid overload and pulmonary edema given he was 1 liter positive on his fluid balance for the prior 24 hours and remained anuric on CRRT, but efforts to remove volume via CRRT were complicated by the development of rapid atrial fibrillation and hypotension which made it difficult to achieve a negative fluid balance. His vasopressor requirements increased from one to three (norepinephrine, phenylephrine, and vasopressin). At 48 hours post-tPA his P/F was 188-250, similar to his pre-tPA status. His fibrinogen levels remained similar at 351 mg/dl and his D-dimer

had decreased to 16,678 ng/ml. Unfortunately, by HD 11 the patients continued to descend into multiple organ failure with refractory hypotension secondary to arrhythmia and superimposed bacterial infection. He was made DNR and expired shortly after.

Case 2

59 year-old female with a history of hypertension presented to an outside hospital after two days of rhinorrhea, cough, myalgias, and headaches. Vital signs from her initial presentation at the outside hospital are not available. CT chest demonstrated bibasilar predominantly ground glass opacities and COVID-19 testing was positive. Hydroxychloroquine and azithromycin were initiated. Her oxygen requirement progressed over two days from nasal cannula O2 supplementation to 100% NRB with a PaO2 of 137. On HD 4 she required intubation for hypoxemic respiratory failure and was transferred to our hospital. She required one vasopressor for hemodynamic support and chemical paralysis in addition to sedation. Her P/F ratio was 82 supine and improved to the 130's in the prone position. On return to supine position her P/F ratio dropped back to as low as 90. On HD 6 her D-dimer was 545 ng/ml and this increased to 20,293 ng/ml by HD 9 with a fibrinogen level of 939 mg/dl. After 4 days of being intubated and 2 days in the prone position with no durable improvements, IV tPA (Alteplase) was administered as a 25mg intravenous bolus over 2 hours, followed by a 25mg tPA infusion over the subsequent 22 hours. The patient tolerated tPA therapy and was transitioned to heparin therapy (as in Case 1) without any bleeding complications. At 4 hours after completing tPA her P/F was 135 (prone position) which was similar to pre- tPA, but by 12 hours after completing tPA her P/F ratio had improved to 150 (prone

position) with D-dimer increased to 40,490 ng/ml. By 38 hours after completing the tPA infusion the patient continued to improve and was placed back in the supine position where the P/F ratio was now 135, a 50% improvement in supine position P/F ratio compared to the P/F of 90 in the supine position three days earlier.

Case 3

49 year-old male with no known medical history presented with 6 days of cough, progressive dyspnea, fever, and myalgias. Vital signs on presentation were T 36.5° Celsius, HR 133 bpm, BP 115/74 mm Hg, RR of 24. SpO2 was 40% on room air in the Emergency Department and improved to 90% on 100% FiO2 via NRB, however given increased tachypnea he was intubated and required one vasopressor for hemodynamic support, sedation and chemical paralysis. A CT chest was performed and revealed bibasilar ground glass opacities. Positive end-expiratory pressure (PEEP) of 20 was initially used, however he developed pneumopericardium and thus his PEEP was reduced. Hydroxychloroquine and azithromycin were started as well as heparin drip for suspicion of venous thromboembolism. On HD 1 his D-dimer was 33,228 ng/ml and on HD 2 had reduced to 17,301 ng/ml. His P/F ratio was 120 in the prone position, and in the supine position his P/F ratio ranged from 72-90. His heparin drip was held and IV tPA (Alteplase) was administered similarly to as in Cases 1 and 2, with the heparin drip resuming immediately after completion of the tPA infusion. His supine P/F improved from 72-90 pre-tPA to a P/F of 125 by 3 hours after completion of tPA, a 38-73% increase. There were no bleeding complications. After tPA, his D-dimer increased from 17,301 ng/ml to 37,215 ng/ml and his fibrinogen decreased from 874 mg/dl (pre-tPA) to

544 mg/dl (35 hours post-tPA). By 33-hours after completing the tPA infusion his P/F ratio declined to 71 and the patient was placed back in the prone position with recovery to a P/F ratio of 118.

DISCUSSION

In summary, we now report 3 cases of off-label intravenous administration of tPA (Alteplase) for patients with COVID-19 suffering from ARDS and respiratory failure. In all 3 cases the patients demonstrated an initial improvement in their P/F ratio, with improvements ranging from a 38% improvement (Case 3) to a ~100% improvement (Case 1). The observed improvements were transient and lost over time in all 3 patients after completion of their tPA infusion. In the study by Hardaway et al using fibrinolytic therapy in ARDS, they re-dosed the fibrinolytic agent in patients who had transient responses such as were observed here, which led to more durable responses (*8*). There is also precedent for using much larger bolus doses of tPA and doing so while patients remain on a therapeutic heparin drip, such as in sub-massive pulmonary embolism where the use of a 100mg bolus of tPA (Alteplase) while on a therapeutic heparin drip has been shown to be highly effective in reducing mortality and only increases bleeding risk by 1.2% (11). Such an approach using larger bolus-dose tPA (50mg or 100mg bolus) without holding anticoagulation in order to prevent recurrence of the suspected pulmonary microvascular thrombosis underlying COVID-19 ARDS (*7*) is worthy of further consideration and study, and while the mortality in COVID-19 ARDS is exceptionally high the risks of tPA must still be carefully considered given the ~1% risk of catastrophic bleeding from tPA in non-stroke patients (*11,12*). Formal studies are

needed to determine whether the observations in these cases were the result of tPA therapy or the result of unrelated/random effects, and (if effective) to determine the optimal dosing regimen of tPA with or without therapeutic anticoagulation in COVID-19 ARDS to include whether a re-dosing protocol is needed if the benefits are transient.

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