tPA Study

PI Name: Daniel Talmor MD MPH

Project Title: STARS ("STudy of Alteplase for Respiratory failure in SARS-Cov2 (COVID-19)", a Phase IIa Clinical Trial

NCT Information: NCT04357730

Study Contact Name/Beeper: Daniel Talmor / 32178

Study Population: Adult patients admitted to ICU
Severe respiratory failure (persisting PaO2/FiO2 ratio < 150 (>4 hours) despite ventilatory support)
COVID+

Treatment Summary: Step-wedge design comparing the following 3 regimens:

1. 50 mg of tPA IV bolus over 2 hr (10 mg push followed 40 mgs over remainder 2hr) + heparin drip.
2. 100 mg of tPA IV bolus administration over 2 hr (10 mg push followed by 90 mg over remaining 2 hr) + heparin drip.
3. Control: standard of care

Key Inclusion criteria:
1. Adult patients ages 18-75 years old
2. Known or suspected COVID-19 infection
3. PaO2/FiO2 ratio < 150 or inferred PaO2/FiO2 ratio from SpO2 if ABG is unavailable, persisting for >4 hours, despite maximal mechanical ventilation management

Key Exclusion Criteria:
- New or recent pulmonary embolism
- Active bleeding
- Recent surgery or trauma
- Pregnancy

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Project Summary

OBJECTIVE: To evaluate the change in respiratory function (PaO2/FiO2 from pre-to-post intervention at 48 hours post randomization) in acutely ill patients with COVID-induced ARDS receiving two different doses of tPA compared to standard of care.

RATIONALE: A new therapeutic approach capable of rapidly treating and attenuating ARDS secondary to COVID-19 is urgently needed.

The dominant pathologic feature of viral-induced ARDS is fibrin accumulation in the microvasculature and airspaces. Substantial preclinical work suggests antifibrinolytic therapy attenuates infection provoked ARDS.

In 2001, a phase I trial demonstrated the Urokinase and Streptokinase were effective in patients with terminal ARDS, markedly improving oxygen delivery and reducing an expected mortality in that specific patient cohort from 100% to 70%.

A more contemporary approach to thrombolytic therapy is tissue plasminogen activator (t-PA) due to its higher efficacy of clot lysis with comparable bleeding risk.

We therefore propose a phase IIa clinical trial with three intravenous tPA treatment arms to improve respiratory function and oxygenation. Additional secondary outcomes will include duration of mechanical ventilation and survival.

DESIGN: This is a Phase IIa clinical trial, open label, multi-center study with a modified stepped-wedge design, testing systemic administration of fibrinolytic therapy with alteplase (tPA) versus standard of care for patients infected with COVID-19 resulting in severe respiratory failure.

TREATMENT: The stepped-wedge randomization scheme is as follows: the first 10 patients will be randomly assigned to Group tPA50 (n=5) or Control (Standard-of-care) (n=5), at which time the first interim analysis occurs. If no stopping criteria are met, the next 10 patients are randomly assigned to Group tPA100 (n=5) or Control (n=5) when the second interim analysis is done. If no criteria for stopping or dropping an arm are met, the next 10 patients are randomly assigned to Group tPA50 (n=5) or Group tPA100 (n=5) when the third interim analysis is done. Finally, if no criteria for stopping or dropping an arm are met, the trial progresses with patients being randomized to Group tpa50 (n=10) or Group tpa100 (n=10) up to the final analysis at n=50.

Group tPA50 (n=20) will receive 50 mg of tPA intravenous bolus administration over 2 hours, given as a 10 mg push followed by the remaining 40 mgs over a total time of 2 hrs. Immediately following the tPA infusion, 5000 U of UFH will be delivered and the heparin drip will be continued to maintain the activated partial thromboplastin time at 60-80sec (2.0 to 2.5 times the upper limit of normal). This tPA protocol is a modification of the GUSTO I to III trials.

Group tPA100 (n=20) will receive 100 mg of tPA intravenous bolus administration over 2 hours, given as a 10 mg push followed by the remaining 90 mgs over a total time of 2 hrs. Immediately following the tPA infusion, 5000 U of UFH will be delivered and the heparin drip will be continued to maintain the activated partial thromboplastin time at 60-80sec (2.0 to 2.5 times the upper limit of normal). This tPA protocol is similar to that used by Konstantinides et al.

Control: standard of care according to the institution’s protocol for ARDS

Re-bolusing of tPA, at the same dose, is permitted in the intervention groups in those patients who show an initial transient response (>20% improvement of PaO2/FiO2 over pre-infusion of alteplase, that is not sustained up to 24 hours after randomization); the repeat dose will be given only 24 hours after the initial tPA administration.

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Key Exclusion Criteria:
- New or recent pulmonary embolism
- Active bleeding
- Recent surgery or trauma
- Pregnancy
- Stroke
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<td>1. Active bleeding or elevated bleeding risk:</td>
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<td>a. INR &gt; 1.7 (with or without concurrent use of warfarin)</td>
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<td>b. Platelet count &lt; 100 x 10^9/L or history of HITT</td>
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<td>c. Fibrinogen &lt; 300mg/dL</td>
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<td>d. Known abdominal or thoracic aneurysm</td>
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<td>e. Major surgery or major trauma within the past 2 weeks</td>
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<td>f. GI or GU bleed within the past 3 weeks</td>
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<td>g. Known bleeding disorder</td>
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<td>h. Arterial puncture at a non-compressible site within the past 7 days</td>
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<td>i. Lumbar puncture within past 7 days</td>
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<td>j. Currently on ECMO</td>
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<td>k. CVA (stroke), history of severe head injury within prior 3 months, or prior history of intracranial hemorrhage</td>
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<td>l. Seizure during pre-hospital course or during hospitalization for COVID-19</td>
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<td>m. Acute myocardial infarction or history of myocardial infarction within the past 3 weeks or cardiac arrest during hospitalization</td>
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<td>n. Hemodynamic instability with Noradrenaline &gt;0.2mcg/Kg/min</td>
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<td>o. Acute renal failure (escalating renal failure with creatinine &gt;3 times baseline)</td>
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<td>p. Liver failure (escalating liver failure with ALT &gt; 3 times baseline)</td>
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**Co-enrollment in other trials permitted?**

YES, co-enrollment is permitted with other trials.