Randomized Clinical Trial of Activated Protein C for the Treatment of Acute Lung Injury

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Online Data Supplement

Online Supplement

Participants. Study exclusion criteria are presented in Table 1. Of note, post-operative patients with single organ failure were excluded starting in March 2005, based on the results of the ADDRESS trial, which suggested that this patient population had an increased risk of death with APC administration (1).

Study Design/Interventions. Randomization was stratified by the presence of sepsis. The infusion was held for 2 hours prior to any invasive procedure and for up to 12 hours after the invasive procedure, depending on the nature of the procedure.

Data Collection. Our study was originally powered to detect a difference in pulmonary dead space fraction because the hypothesized mechanism of APC for the treatment of ALI involves an improvement in pulmonary blood flow and ventilation to perfusion matching. We assumed a mean dead space fraction in the control group of 0.58 with a standard deviation of 0.10 based on the results of Nuckton et al (2). With the planned enrollment of 90 patients (45 patients per study arm), the original study had a statistical power of 80 percent to detect an absolute treatment effect of APC on pulmonary dead space fraction of 0.06 compared with the placebo group, or a 10% relative reduction in dead space fraction. However, when reviewing our Investigational New Drug application, the FDA concluded that a more clinically relevant endpoint was needed and strongly recommended a change in the primary endpoint to ventilator free days with pulmonary dead space fraction retained as a secondary endpoint. Based on the mean number of days without ventilator use reported in the ARDS Network low tidal volume ventilation study (3),our study was therefore powered to detect a 6.5 day difference in the number of days without ventilator use between the two groups

Interim analyses at 30 and 60 patients were planned to review safety data given the known risk of bleeding with activated protein C. Given the modest size of this trial and our limited power, we did not anticipate that the study would be terminated early for efficacy or futility, and therefore formal stopping rules were not pre-set. Nonetheless, the Data Safety Monitoring Board elected to stop the study after the second interim analysis because they concluded that inclusion of an additional 15 patients was unlikely to significantly alter the results of the study. Given the known risk of bleeding with activated protein C, they were concerned that the small likelihood that a life-threatening bleeding event would occur in the next 15 patients outweighed any potential scientific benefits.

The lung injury score, a composite of oxygenation (PaO2/FiO2 ratio), the level of PEEP, respiratory compliance, and the extent of opacification on the chest radiograph, was calculated as described in (4). When the respiratory compliance measurement was not available, the lung injury score was calculated based on the other 3 components. For organ failure free days calculations, missing data were treated as normal.

Measurements. Interleukin-6 was measured using a two-antibody sandwich enzyme linked immunosorbent assay (ELISA) obtained from R&D Systems (Minneapolis, MN). PAI-1 was measured using a commercially available ELISA from American Diagnostica (Stamford, CT) as in (5). Protein C was measured using a commercially available ELISA from Helena Laboratories (Beaumont, TX) as described previously (6). Pulmonary dead-space fraction was measured using the NICO® Cardiopulmonary Management System (Novametrix, Wallingford, CT). This device uses volumetric capnography(7) to calculate

the partial pressure of mixed expired CO_2, which is then used in the Enghoff modification of the Bohr equation (8): Dead space fraction = $(PaCO_2 - P_ECO_2)/PaCO_2$

Adverse events. Severe adverse events were defined as any untoward clinical event that is fatal or immediately life-threatening, that is permanently or severely incapacitating, that prolongs hospitalization, or any medical event that could require intervention to prevent one of the serious outcomes listed above, regardless of whether or not the event was judged to be related to the study drug infusion. There were no intracerebral severe adverse bleeding events.

References

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Supplemental Table E1: Exclusion criteria

1. Family / patient refuses
2. Patient / surrogate unavailable
3. Attending refuses
4. Age less than 18 years
5. Severe sepsis with APACHE II score ≥ 25 and within 48 hours of onset of severe sepsis
6. Greater than 72 hours since all inclusion criteria are met.
7. Neuromuscular disease that impairs ability to ventilate without assistance, such as C5 or higher spinal cord injury, amyotrophic lateral sclerosis, Guillain-Barré syndrome, myasthenia gravis, or kyphoscoliosis.
8. Pregnancy (negative pregnancy test required for women of child-bearing potential).
9. Severe chronic respiratory disease
10. Weight > 160 kg.
11. Burns greater than 30% total body surface area.
12. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated to be greater than 50%.
13. Bone marrow transplant within the last 5 years
14. Not committed to full support.
15. Severe chronic liver disease (Child-Pugh Score of 11 -15)
16. Diffuse alveolar hemorrhage from vasculitis.
17. Participation in other experimental medication trial within 30 days
18. Patients who have already received APC therapy during this hospitalization
19. Active internal bleeding.
20. Recent hemorrhagic or ischemic stroke (within 3 months).
21. Recent intracranial or intraspinal surgery or severe head trauma (within 2 months).
22. Trauma with an increased risk of life-threatening bleeding.
23. Presence of an epidural catheter.
24. Intracranial neoplasm mass lesion or evidence of cerebral herniation.
25. Patients at high risk of intracranial hemorrhage as evidenced by any of the following: (A) Intracranial or spinal pathology putting them at risk for intracranial hemorrhage (for example, arterio-venous malformation, previous intracranial bleeding events). This does not include patients with meningitis. (B) Acute change in neurological status with focal neurological findings. (3) Documented intracranial hypertension by lumbar puncture or imaging. (4) Seizures in which there is a clinical suspicion of intracranial hemorrhage.
26. Known bleeding diathesis.
27. Concurrent therapeutic heparin (> 14 units/kg/hr)
28. Platelet count < 30,000 x 10^6/L, even if the platelet count is increased after transfusions
29. Prothrombin time – INR > 3.0.
30. Recent (within 6 weeks) gastrointestinal bleeding.
31. Concurrent need for systemic anticoagulation with therapeutic unfractionated heparin or low molecular weight heparin during the study drug infusion

32. Concurrent administration of an anticoagulant (other than subcutaneous heparin for prophylaxis)
33. Concurrent need for platelet glycoprotein IIib/IIIa antagonists or any other antiplatelet agents (patients taking aspirin or another antiplatelet agents at baseline are eligible provided it can be discontinued during study drug infusion)
34. Surgery within 30 days and single organ failure
35. Surgery within 12 hours