

Activated Protein C versus placebo in the treatment of Inflammatory or Infectious ALI/ARDS (INFALI): a pathophysiological study on pulmonary microvascular permeability, apoptosis, inflammation and coagulation.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21017

Source

NTR

Brief title

INFALI

Health condition

Acute Lung Injury (ALI), Acute Respiratory Distress Syndrome (ARDS)

Sponsors and support

Primary sponsor: VU University Medical Center (VUmc), department of Intensive Care

Intervention

Outcome measures

Primary outcome

67-Gallium pulmonary leak index (PLI)

Secondary outcome

1. Lung Injury Score
2. inflammatory mediators/biomarkers (blood, mini-BAL)
3. coagulation and fibrinolysis markers (blood, mini-BAL)
4. apoptosis markers (blood, mini-BAL)
5. mortality
6. extra-vascular lung water
7. gas exchange (compliance, PaO₂/FiO₂)
8. radiographic abnormalities (X-ray, CT)
9. change of ventilatory mode (noninvasive vs. invasive)
10. duration of mechanical ventilation

Study description

Background summary

Background:

Activated protein C (aPC), an endogenous plasma serine protease with antithrombotic, profibrinolytic and anti-inflammatory properties, is a very important modulator of the host response to infection. Drotrecogin alfa (recombinant activated protein C) was shown to reduce 28-day all cause mortality in patients with severe sepsis and to have an acceptable safety profile. The uncontrolled coagulation combined with uncontrolled systemic inflammation, which may lead to multiple organ dysfunction and lethal septic shock, are the primary targets of intervention with aPC.

In acute lung injury and the adult respiratory distress syndrome (ALI and ARDS, respectively) several features similar to sepsis are found such as microvascular thrombosis and a disrupted protein C system, both determinants of outcome in these patients. Considering these circulatory and intra-alveolar derangements which clearly contribute to the pathogenesis of

ALI/ARDS (increased pulmonary dead space, decreased pulmonary blood flow) the protein C pathway could be a therapeutic target in ALI/ARDS. Because aPC is known to have anti-coagulant and anti-inflammatory properties it is plausible that aPC may have value in the treatment of patients with ALI from infectious and non-infectious origin.

Hence, our hypothesis is that systemic aPC will benefit patients with ALI/ARDS, as caused by inflammatory as well as infectious disorders, in terms of gas exchange, edema and capillary leak in these lungs, as well as in ventilator-days (duration of mechanical ventilation) or change in ventilatory mode.

Aim of this study:

The primary aim of our study is to investigate the effect of aPC versus placebo on pulmonary microvascular permeability, extra-vascular lung water, gas exchange, the severity of lung injury, mode of ventilation and radiographic abnormalities in patients with ALI/ARDS by either infectious causes (septic patients with single organ respiratory failure) or by inflammatory causes (pulmonary contusion, toxic, pancreatitis, vasculitis, etc). We will primarily stratify patients according to their etiology (infectious versus inflammatory) and secondly to the mode of ventilatory support (mechanical ventilation, noninvasive ventilation, spontaneous breathing). In addition, we will assess inflammatory, coagulation and fibrinolysis markers in both the systemic circulation as well as the alveolar compartment (when mechanically ventilated).

Design:

We will randomize 106 patients with ALI/ARDS with different etiologies to receive either aPC (24 mcg/kg/hr) or placebo during (in total) 96 hours by continuous infusion. We aim to include different patient groups depending on their ventilatory support (spontaneous, non-invasive and invasive ventilation). The treatment setting will be either the Medium Care as well the Intensive Care. Two centers will be participating: VUmc and AMC.

Before, during and after treatment with aPC/placebo different parameters will be investigated: clinical characteristics, disease severity, laboratory markers inflammatory, coagulation, apoptosis), radiological features, lung injury scores, mini-broncho-alveolar lavages (mini-BALs), and pulmonary microvascular permeability.

Strict safety monitoring will take place as well as strict stopping rules will be applied.

Primary endpoint:

microvascular permeability (67 gallium-transferin pulmonary leak index)

Secondary endpoints:

Lung Injury Score (LIS)

gas exchange

radiography (X-ray, CT)

ventilatory mode (change)

duration of ventilation

inflammatory mediators (blood, lung)

coagulation and fibrinolysis (blood, lung)

apoptosis (blood, lung)

Study objective

We hypothesize that systemic aPC will benefit patients with ALI/ARDS, as caused by inflammatory as well as infectious disorders, in terms of gas exchange, edema and capillary leak in these lungs, as well as in ventilator-days (duration of mechanical ventilation) or

change in ventilatory mode.

Intervention

After stratification patients will be randomly assigned to the aPC (24 mcg/kg/hr during (in total) 96 hrs) or placebo group.

1. On day 1 and 5 a 67-Ga Pulmonary Leak Index and a CT-Thorax will be performed
2. In mechanically ventilated patients: mini broncho alveolar lavage every second day
3. Day 1-5, 7, 9, 11, 13, 15 blood samples and a chest X-ray

Contacts

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Scientific

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Eligibility criteria

Inclusion criteria

1. age 18 - 75 years

2. weight < 135 kg
3. recent onset (<24 h) of ALI/ARDS, according to the American/European consensus criteria
4. ALI/ARDS due to severe sepsis reflecting single organ failure

Exclusion criteria

1. APACHE II score: 25 and more
2. 2 or more failing organs
3. thrombocytecount < $30 \times 10^9/l$
4. Any major surgery within 12 h before inclusion
5. Trauma patients at increased risk of bleeding
6. Acute bleeding
7. A history of severe head trauma that required hospitalization, intracranial surgery, or stroke within 3 months of study entry
8. Known intracranial abnormality such as aneurysms, tumor, arterio-venous malformation
9. Known hypercoagulability:
 - 9.1 Resistance to protein C
 - 9.2 Hereditary deficiency of protein C, protein S, or antithrombin
 - 9.3 Presence of anticardiolipin antibody, antiphospholipid antibody, lupus anticoagulant or homocystinemia
 - 9.4 Recently documented (within 3 months of study entry) or highly suspected deep vein thrombosis or pulmonary embolism
10. A history of congenital bleeding diathesis
11. Expected life expectancy less than 28 days (moribund state)
12. Preterminal illness
13. Pregnancy or breast feeding

- 14. Known portal hypertension with liver cirrhosis, esophageal varices or both
- 15. Epidural catheter
- 16. Body weight >135 kg
- 17. Chronic renal insufficiency
- 18. Participation in another clinical trial
- 19. Patients with immune system impairment
 - 19.1 HIV-infected patients (CD4+ < 50/ml)
 - 19.2 After bone-marrow, lung, liver, pancreas or small-bowel transplantation and treated with immunosuppressive therapy

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Masking:	Single blinded (masking used)
Control:	Placebo

Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	01-09-2006
Enrollment:	106
Type:	Anticipated

Ethics review

Positive opinion	
Date:	01-08-2006
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL735
NTR-old	NTR745
Other	: N/A
ISRCTN	ISRCTN52566874

Study results

Summary results

will be written after analysis of results