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.

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Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON21017

Bron
Nationaal Trial Register

Verkorte titel
INFALI

Aandoening

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

Ondersteuning

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

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

67-Gallium pulmonary leak index (PLI)

Toelichting onderzoek

Achtergrond van het onderzoek

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)

Doel van het onderzoek

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.

Onderzoeksproduct en/of interventie

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 broncheo alveloar lavage every second day

3. Day 1-5, 7, 9, 11, 13, 15 blood samples and a chest X-ray

Contactpersonen

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. APACHE II score: 25 and more

2. 2 or more failing organs

3. thrombocytecount < 30 * 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 diasthesis

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

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Blindering:	Enkelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-09-2006
Aantal proefpersonen:	106
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	01-08-2006
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

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

Resultaten

Samenvatting resultaten
will be written after analysis of results