Effect of Intravenous Administration of Recombinant Human Activated Protein C on Local Inflammation and Coagulation after Bronchial Instillation of House Dust Mite Allergen and Lipopolysaccharide in Asthma Patients

Published: 11-04-2011
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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON35983

Source
ToetsingOnline

Brief title
ACHILLES study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Asthma

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Nederlands Astma Fonds

Intervention

Keyword: allergen, asthma, coagulation, Inflammation

Outcome measures

Primary outcome

Eight hours after instillation of HDM and LPS (t = 8 hours) a second

bronchoscopy will be performed and the challenged segments will be lavaged.

Primary outcome is leukocyte difference in obtained lavage fluid.

Secondary outcome

In BAL fluid and blood, obtained directly before bronchoscopies, leukocyte

responses, the response of alveolar macrophages, activation of the cytokine and

chemokine network, complement and activation of coagulation and fibrinolysis

will be determined.

Study description

Background summary

Allergic lung inflammation is associated with reduced bronchoalveolar levels of endogenous activated protein C (APC). The biological effects of APC are pleiotropic, and can be roughly divided in anticoagulant and cytoprotective effects. Recombinant human Activated Protein C (rhAPC) has been shown to decrease inflammation and is known for its capability to decrease mortality of patients with severe sepsis. Recent evidence derived from animal studies, in part from our laboratory, indicates that APC is also beneficial in allergic inflammatory conditions. In this study, we will examine whether intravenous administration of rhAPC is capable to inhibit local inflammation, within a lung subsegment, induced by combined administration of house dust mite (HDM) and

lipopolysaccharide (LPS) in asthma patients.

Study objective

The primary objective is to determine the effect of intravenously administered rhAPC on HDM-LPS induced allergic lung inflammation.

Study design

Double-blind, randomized controlled single centre intervention study in 28 asthma patients (18 - 45 years).

Intervention

28 asthma patients will start on intravenous treatment with rhAPC or placebo 4 hours before (t = -4 hours) bronchial instillation of HDM/LPS in a lung subsegment and bronchial instillation of saline in a contralateral lung subsegment (t = 0 hours). Intravenous treatment with rhAPC or placebo will be continued until 1 hour before initiation of the second bronchoscopy.

Study burden and risks

The burden associated with this study includes a screening visit, during which an intake interview, a physical examination, routine blood tests and spirometry will be done. After a medication free period of 2 weeks, subjects will stay in the hospital overnight. At 5.00 AM (t = -4 hours) intravenous infusion of rhAPC or placebo will be started; two bronchoscopies will be done (at t = 0 hours and t = 8 hours), which in our own experience is very well tolerated. At t = -4 hours and before each bronchoscopy blood will be obtained (60 ml each). Bronchial instillation of HDM/ LPS may induce bronchus obstruction in patients. This will be monitored by spirometry and Salbutamol (Ventolin by inhaler) will be available as rescue medication during the study for all subjects. Notably, our department has experience with both LPS challenge and HDM/LPS challenge by bronchoscope in asthma patients (METC 08/241); these challenges are well tolerated. RhAPC is registered for intravenous use; the risks associated are minimal. The low risk and little discomfort outweigh the potential benefit generated by this proof-of-principle study. The results of this study may be important for asthma patients as it will shed light on the effect of APC on allergic inflammation and coagulation in asthma and on a potential new therapeutic approach for asthma in general. Furthermore, this study will provide data which could clarify how HDM and LPS exert their effects on lung inflammation in asthma patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Intermittent to mild asthmatics between 18 and 45 years of age according to the Global Initiative for Asthma (GINA) criteria
* Allergy for HDM documented by a positive RAST and a positive skin prick test.
* No clinically significant findings during physical examination and hematological and biochemical screening
* At spirometry FEV1 more than 70% of predicted value
* Able to communicate well with the investigator and to comply with the requirements of the study
* Stable asthma withouth the use of asthma medication 2 weeks prior to the study day.
* Written informed consent
* No current smoking for at least 1 year and less than 10 pack years of smoking history
* Both male and female subjects are eligible for the study. Female subjects of child bearing

potential will use adequate anti-conceptive precautions and will be tested for pregnancy.

Exclusion criteria

* Relevant comorbidity, pregnancy and/or recent surgical procedures.
* A history of smoking within the last 12 months, or regular consumption of greater than three units of alcohol per day
* Exacerbation and/ or the use of asthma medication within 2 weeks before start
* Administration of any investigational drug within 30 days of study initiation
* Donation of blood within 60 days, or loss of greater than 400 ml of blood within 12 weeks of study initiation
* History of enhanced bleeding tendency or abnormal clotting test results.
* History of heparin-induced thrombocytopenia
* History of serious drug-related reactions, including hypersensitivity
* Inability to maintain stable without the use of asthma medication 2 weeks before start.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-09-2011
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	xigris
Generic name:	Drotrecogin alfa activated
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-04-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 22425
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2011-001543-76-NL
CCMO	NL36336.018.11
OMON	NL-OMON22425

Study results

Date completed:	26-11-2012
Actual enrolment:	28

Summary results
Trial is onging in other countries