The airway smooth muscle cell in asthma:
A genomics approach

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To examine the difference in gene expression profiles of ASM in bronchial biopsy specimens between asthmatic patients, non-asthmatic allergic and non-asthmatic non-allergic controls.To associate the gene expression profiles with airway...

Ethical review	Approved WMO
Status	Pending
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON33978

Source
ToetsingOnline

Brief title
Genomics in asthma

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

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: airway smooth muscle, allergic asthma, RNA whole transcriptome sequencing, serial analysis of gene expression (SAGE)

Outcome measures

Primary outcome

A genomic analysis of the airway smooth muscle layer of asthmatics and healthy, non-asthmatics by using laser capture microdissection (LCM) technique.

Secondary outcome

The gene expression profiles of ASM will be associated with physiologic parameters obtained by lung function tests, eNO, and FOT.

The gene expression profiles of ASM will be associated with biochemical parameters obtained by immunohistochemistry.

The presence and type of bronchial pathogens will be associated with clinical severity, and with the degree and profile of airways inflammation, airway remodelling and airway hyperresponsiveness by viral real-time multiplex PCR and bacterial PCR analysis.

The venous blood gene profile will be associated with the physiological and pathological parameters.

Study description

Background summary

Asthma is a worldwide disease with symptoms that are characteristic and well described. However the pathophysiologic mechanisms leading to the observed functional changes are still unknown. Recently, interest has been shown in the ASM layer as an important structure contributing to the pathophysiologic features of asthma. Several studies have shown that the phenotype of ASM is

changed with asthma and it is postulated that ASM itself can contribute to the regulation and perpetuation of airways inflammation in asthma. Mast cells and progenitor cells of the ASM also tend to play an important role in asthma. Furthermore, the beneficial effects of corticosteroids on the clinical status and lung function are well described. However it is not clear whether this is solely based on its anti-inflammatory effect or that steroids also have other local actions . Therefore, the airway smooth muscle layer could be the common pathway in determining variable airways obstruction in asthma. We hypothesize that the phenotypic profiles of the ASM layer at the gene-level is different between asthmatic and healthy patients, is associated with measures of variable airways obstruction and with the inflammatory infiltrate within the ASM layer, and that the ASM gene expression profile changes after treatment with oral steroids.

Study objective

To examine the difference in gene expression profiles of ASM in bronchial biopsy specimens between asthmatic patients, non-asthmatic allergic and non-asthmatic non-allergic controls.
To associate the gene expression profiles with airway hyperresponsiveness, dynamics of airway resistance, and inflammatory cell infiltrates in- and outside the ASM layer in asthma.
To investigate the change in gene expression profiles in relation to clinical and functional improvement after 14 days of oral steroids treatment.
To associate the presence and type of bronchial pathogens with clinical severity, and with the degree and profile of airways inflammation, airway remodelling and airway hyperresponsiveness.
To examine the ASM volume in biopsy specimens in asthmatic and non-asthmatic patients.
To associate the physiologic and pathologic parameters of asthma with the circulating venous blood gene profile.
To maximize the quality of the data in asthmatic patients and controls through confirmation of the feasibility of RNA-analysis by using biopsy material obtained from chronic cough patients.

Study design

The study consists of three different study phases: screening, study phase 1 and study phase 2.
A cross-sectional study will be done during study phase 1, and a randomised controlled, double-blind, parallel intervention study during study phase 2.

Furthermore, prior to the study, the feasibility of RNA-analysis will be confirmed by using biopsy material of chronic cough patients.

Intervention

During study phase 2, the asthmatic patients will be randomly divided in 2 groups of equal sizes. One group will receive an oral steroid (Prednisolone) and the other group placebo.

Study burden and risks

All study procedures will be carried out on an international consensus basis and performed by qualified personnel.
The amount of procedures and duration of the study depends on the patientgroup:
Asthmatic patients in 2 months: once a general physical examination and skin prick test during screening, 3 times spirometry, 2 times FOT and eNO measurements, 2 times methacholine bronchoprovocation test, 2 times venous blood collection and bronchoscopy with biopsies. The bronchoscopy will always be preceded by blood collection. The time between the 2 bronchoscopies will be at least 14 days.
Non-asthmatic, healthy patients in 1 month: once a general physical examination and skin prick test during screening, 2 times spirometry, once a FOT an eNO measurement, once a methacholine bronchoprovocation test, once a venous blood collection and bronchoscopy with biopsies.The bronchoscopy will always be preceded by peripheral blood collection.

After a bronchoscopy, patients could develop a slight amount of recurrent bleeding, which most of the time will be self-limiting. Regardless, the patient will stay at the AMC for at least an hour after the bronchoscopy has been done. Only with permission of the attending physician the patient is allowed to go home. Patients could develop a short term fever (couple of hours). Most of the time it will be resolved by the next day. The patient will otherwise be advised to contact his or her general practitioner or attending physician.
During venous blood collection, the patient may experience light-headedness. This will be attenuated as much as possible by instructing the patient and making the procedure as comfortable as possible, for example sitting in a comfortable chair. However, light-headedness is not expected to occur frequently as 2,5ml of blood will be collected.
It is known that Prednisolone given orally may be accompanied by systemic side effects. Patients will be asked to report all side-effects during these 14 days of dosing as soon as possible. If deemed necessary after review, the patient will immediately stop taking the medication and the clinical status wil be followed-up to ensure his or her safety. The dosage and dosing scheme used in this study has been recommended as exacerbation treatment. In other words, patients will receive only one extra episode of exacerbation treatment by participating in this study.

Regarding confirming the feasibility of RNA-analysis, one extra biopsy specimen will be taken from chronic cough patients, who are scheduled to undergo a routine, diagnostic bronchoscopy with biopsy collection. The collection of one extra biopsy specimen wil have no influence on the results of the bronchoscopy. Furthermore, the execution of the bronchoscopy will not differ from the normal

situation.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
1105AZ Amsterdam
Nederland
Scientific
Academisch Medisch Centrum

Meibergdreef 9
1105AZ Amsterdam
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Asthmatic patients :
- Age between 18 * 50 years
- History of episodic chest tightness and wheezing
- Intermittent or mild persistent asthma according to the criteria by the Global Initiative for Asthma
- Non-smoking or stopped smoking more than 12 months ago and 5 pack years or less
- Clinically stable, no exacerbations within the last 6 weeks prior to the study. Occasional usage of inhaled short-acting Beta2-agonists as rescue medication is allowed, prior and during the study.

- Steroid-naïve or those patients who are currently not on corticosteroids and have not taken any corticosteroids by any dosing-routes within 8 weeks prior to the study
- Baseline FEV1 >70% of predicted
- Airway hyperresponsiveness, indicated by a positive methacholine challenge with PC20 <8mg/ml
- Positive skin prick test (SPT) to one or more of the 12 common aeroallergen extracts, defined as a wheal >3mm in diameter;Healthy, non-asthmatic patients are recruited using the following inclusion criteria:
- Age between 18 * 50 years
- Non-smoking or stopped smoking more than 12 months and 5 pack years or less
- Baseline FEV1 >70% of predicted
- Negative methacholine challenge or PC20 >8mg/ml
- No usage of steroids by any dosing route
Additionally, non-asthmatic non-allergic patients must have a negative skin prick test (SPT) to one of the 12 common aeroallergen extracts, whereas non-asthmatic allergic patients must have a positive SPT.;Regarding confirming the feasibility of RNA-analysis:
- Chronic cough patients who are scheduled to undergo a routine, diagnostic bronchoscopy with biopsy collection.

Exclusion criteria

- History of clinical significant hypotensive episodes or symptoms of fainting, dizziness, or light-headedness
- Women who are pregnant or lactating or who have a positive urine pregnancy test at screening
- Chronic use of any other medication for treatment of lung disease other than short-acting Beta2-agonists
- Ongoing use of tobacco products of any kind or previous usage with a total pack year of 6 or greater

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2008
Enrollment:	48
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Prednisolone
Generic name:	Prednisolone

Ethics review

Approved WMO Date:	16-07-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2009
Application type:	Amendment
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: 24761
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2008-001644-38-NL
CCMO	NL22615.018.08
OMON	NL-OMON24761