A better understanding of molecular mechanisms leading to asthma and its remission.

Published: 20-10-2015
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Objective: to determine the underlying mechanisms and molecular events leading to remission of asthma.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON45213

Source
ToetsingOnline

Brief title
Asthma origins and remission study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
asthmatic bronchitis, Bronchitis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,GlaxoSmithKline

Intervention

Keyword: Asthma, genetics, Inflammation, Remission

Outcome measures

Primary outcome

The primary endparameter will be the difference in the transcriptomic profile of innate lymphocytes, CD4+ T cells, and CD8+ T cells and epithelial cells in bronchial biopsies and of blood eosinophils obtained from subjects with ongoing asthma, clinical or complete asthma remission and healthy controls.

Secondary outcome

Questionnaires

Questionnaires will be the ELON questionnaire, the Asthma Control Questionnaire (ACQ), and the small airways dysfunction tool (SADT).

Spirometry measurements: FEV1, FVC, FEF25, FEF50, FEF75 and FEF25-75.

Body plethysmography: TLC, RV, FRC, VC, IVC. Specific airway conductance (sGaw), airway resistance (Raw).

Impulse oscillometry (IOS): Parameters assessed with this test are: R5, R20, X5, R5-R20.

Skin prick test for allergy

Peripheral blood

• Hemoglobin, leucocytes and differentiation, thrombocytes (10 mL peripheral blood; EDTA tube).

• DNA and plasma (10 mL peripheral blood; EDTA tube).

• RNA (10 mL, PAXgene tube)

• Serum (10 mL peripheral blood serum tube).

• Total IgE, Phadia-top and CRP will be measured in serum (10 mL peripheral blood serum tube).

• PBMCs (40mL peripheral blood; heparin lithium tubes).

Methacholine and Adenosine Monophosphate (AMP) provocation

HRCT scan of the thorax

Multiple Breath Nitrogen Washout (MBNW): Parameters assessed are LCI, Sacin, Scond.

Exhaled Nitric Oxide (single breath at multiple flows)

PExA: Particles in exhaled air.

Inflammatory cell counts in bronchial biopsies and induced sputum.

mRNA, non-coding small and large RNA, and DNA methylation in bronchial and

brushes, nasal epithelial brushes.

Study description

Background summary

Asthma is characterized by chronic airway inflammation of the large and small airways. Asthma patients often have episodes with symptoms of dyspnea, wheezing and nocturnal awakening. Currently available inhaled anti-inflammatory treatments reduce the airway inflammation and treatment but do not cure the disease. Therefore asthma patients often need life-long treatment to control their asthma.

In a small subset of patients, their asthma resolves spontaneously. This phenomenon is called asthma remission. Subjects with asthma remission do not experience symptoms or signs of airway inflammation anymore and do not require inhaled treatments. Some subjects with asthma remission also have a completely normal lung function without signs of bronchial hyperresponsivess: they have complete asthma remission. Unfortunately, asthma remission occurs only in a small subset of 15-25% of asthma patients.

Study objective

Objective: to determine the underlying mechanisms and molecular events leading to remission of asthma.

Study design

This will be a single-center, non-pharmacological intervention, cross-sectional study.

Subjects will be evaluated as follows:
Visit 1: Demographics, Pregnancy test (if applicable), Spirometry and reversibility with sputum induction, Symptom questionnaires (CCQ, RAND-36, SQUASH ACQ, St. Georges, Comorbidity (ACE-27), Smoking Questionnaire), peripheral blood collection.
Visit 2:, ECG, Multiple Breath Nitrogen Washout test (MBNW), bronchial and alveolar exhaled nitric oxide, body box and diffusion capacity, IOS, methacholine provocation test, PExA.
Visit 3: AMP provocation test, skin prick test.
Visit 4: Peripheral blood collection, Nasal brush, in- and expiratory CT scan followed by bronchoscopy, which is carried out during conscious sedation, bronchoscopy experience questionnaire.

Study burden and risks

Risks for participants in this study are:
1. Developing or worsening of asthma symptoms
2. Dyspnea during sputum induction and provocation test with methacholine or AMP.
3. Bronchospasm during bronchoscopy and / or desaturation during the bronchoscopy
4. Bleeding during collection of bronchial biopsies, bronchial or nasal brushes.

Measures for treatment or prevention
Ad 1: In previous studies stopping the asthma medication for a short period never led to serious problems.
Ad 2: Before the sputum induction and after the methacholine and AMP provocation every subject will inhale 40 g of ipratropium bromide. This will prevent or treat dyspnea.
Ad 3: If bronchospasms occur during the bronchoscopy the procedure will be stopped immediately and if necessary subject will be given extra bronchodilator medication by inhalation. This will treat bronchospasm properly. Monitoring of oxygen saturation will be performed during the whole procedure and subjects will be given a standard of 4 L/min of oxygen with a nasal cannula as a precaution measure. If necessary the bronchoscopy will be stopped.
Ad4: If hemostasis is necessary, xylometazoline will be applied locally.

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

Inclusion criteria for all subjects:
• Age between 40 and 65 years old.
• Smoking history <= 10 packyears.;Inclusion criterium for asthma remission subjects:
• Onset of asthma symptoms <=21 years.;Specific inclusion criteria for the 4 different groups:
o Group 1. Subjects with clinical asthma remission:
• Documented history of asthma diagnosed according to latest GINA guidelines, i.e. respiratory symptoms and either bronchodilator reversibility (improvement in FEV1 of more than 12% of baseline (and at least 200 mL) after inhalation of 800 µg salbutamol.
• No use of asthma medications such as inhaled or oral corticosteroids, β2-agonists or anticholinergics for 3 years.
• No symptoms of wheeze or asthma attacks during the last 3 years.
o Group 2. Subjects with complete asthma remission
• Documented history of asthma diagnosed according to latest GINA guidelines, i.e. respiratory symptoms and either bronchodilator reversibility (improvement in FEV1 of more than 12% of baseline (and at least 200 mL) after inhalation of 800 µg salbutamol.
• No use of asthma medications such as inhaled or oral corticosteroids, β2-agonists or anticholinergics for 3 years.
• No symptoms of wheeze or asthma attacks during the last 3 years.
• FEV1 > 90% predicted.
• Absence of bronchial hyperresponsiveness, i.e. both PC20 methacholine > 8 mg/ml and PC20 AMP > 320 mg/ml.;o Group 3. Patients with ongoing asthma
• Documented history of asthma diagnosed according to latest GINA guidelines, i.e. respiratory symptoms and either bronchodilator reversibility (improvement in FEV1 of more than 12% of baseline (and at least 200 mL) after inhalation of 800 µg salbutamol.
• Use of inhaled corticosteroids
or
Either persistent symptoms of wheeze, cough, or dyspnea or regular use of β2 agonists at least once a week during the last 2 months.

• PC20 methacholine < 8 mg/ml.
o Group 4. Non-asthmatic controls
• No history of asthma.
• No use of inhaled corticosteroids or β2-agonists for a period longer than 1 month.
• No symptoms of wheeze, nocturnal dyspnea, or bronchial hyperresponsiveness.
• PC20 methacholine > 8 mg/ml, FEV1/FVC > 70% and FEV1 > 80% predicted.

Exclusion criteria

• FEV1 <1.2 L,
• Upper respiratory tract infection (e.g. colds), within 6 weeks.
• Signs or symptoms of severe, progressive or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic or cerebral disease.
• Malignancy within the past 5 years (except for squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence).
• Known recent substance abuse (drug or alcohol).
• Females of childbearing potential without an efficient contraception

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	80
Type:	Anticipated

Ethics review

Approved WMO Date:	20-10-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
CCMO	NL53173.042.15
Other	volgt nog