Towards Targeting the Origin of Asthma: Cross-talk between airway epithelium and immune cells

Published: 05-02-2020
Last updated: 10-04-2024

To determine underlying mechanisms and molecular events in asthma.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON49140

Source
ToetsingOnline

Brief title
ORIENT

Condition

- Bronchial disorders (excl neoplasms)

Synonym
bronchitis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: asthma, genetica, immune, origin

Outcome measures

Primary outcome

Identify key in vivo pathogenic features of airway wall cells in asthma, as reflected by single-cell transcriptomics of primary bronchial epithelial cells (BEC), as well as mesenchymal, endothelial and immune cells.

Secondary outcome

Questionnaires: ELON, ACQ, SADT and post-bronchoscopy questionnaire.

Spirometry: FEV1, FVC, FEF25, FEF50, FEF75, FEF 25-75.

Body box: TLC, RV< FRC, VC, IVC, airway conductance, airway resistance.

Impulse oscillometry: R5, R20, X5, R5-R20.

Skinpricktest for allergies

Blood: Hemoglobin, leukocytes and differentiation, trombocytes. DNA, RNA, total IgE, phadiatop and CRP. PBMCs.

Provocation with methacholine.

HRCT scan

NO measurement in different airflow.

Multiple breath Nitrogen Washout test.

Cell countin sputum.

mRNA, microRNA, long non-coding RNA and DNA methylation in airway biopties and

brushes.

Study description

Background summary

Asthma is characterized by chronic airway inflammation, which is multifactorial in origin. It is a heterogeneous disease, characterized by chronic airway inflammation, mucus hypersecretion, airway hyperresponsiveness, bronchoconstriction and airway wall remodeling. The underlying mechanisms of this complex disease are not yet understood but previous studies find a genetic predisposition. Several lines of evidence indicate that in asthma patients the airway epithelium is primarily affected, including increased basal cell proliferation, a loss of differentiated epithelial cells and reduced numbers of ciliated cells. In order to further identify and study the mechanisms, clinical information and single cell RNA analyses on epithelial cells from the bronchi and nose will combined in this study.

Study objective

To determine underlying mechanisms and molecular events in asthma.

Study design

We will include 78 subjects divided over three groups: asthma patients (52 subjects) of which half stop their medication and half does not, and non-asthmatic healthy controls (26 subjects) in a cross-sectional study. All subjects will be extensively clinically characterized including respiratory symptoms/questionnaires, in- and expiratory CT-scans, and parameters of large and small airway function and inflammation. In addition, blood and nasal epithelial brushes will be obtained to study the genetic and epigenetic mechanisms of asthma. Finally, bronchoscopy with bronchial biopsies and brushes will be performed under conscious sedation. Bronchial biopsies from both patient groups will be used for single cell transcriptional analysis.

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.
3. Bronchospasm during bronchoscopy and / or desaturation during the bronchoscopy.

Measures for treatment or prevention:

Ad 1: Subjects who cease medication in order to partake will perform a baseline spirometry and if there is a fall of 15% in FEV1, subjects will be excluded.
Ad 2: Before the sputum induction and after the methacholine every subject will be given inhaled salbutamol to 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. If necessary the bronchoscopy will be stopped.

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

All groups:

• Age between 18 and 65.

o Group 1. Patients with asthma, GINA step 1-3 (who stop using ICS/LABA in order to partake in the study)
• 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) or PC20 methacholine < 8 mg/ml.
• Use of low or medium dose inhaled corticosteroids, possibly combined with LABA (as GINA step 2-3) at baseline 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 (step 1).

o Group 2: Patients with asthma GINA class 2-5 (who continue using their medication)
• 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) or PC20 methacholine < 8 mg/ml.
• Use of inhaled or oral corticosteroids.
o Group 3: Non-asthmatic controls
• No history of asthma.
• No use of inhaled corticosteroids or β2-agonists for a period longer than 1 month in their lifetime and not during the 6 weeks before inclusion.
• 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,
• Subjects must be able to adhere to the study visit schedule and other protocol requirements.
• A subject is not eligible to enter and participate if he has not signed and dated a written informed consent form prior to participation in the study.
• A subject is not eligible to enter and participate if he does not agree that we inform his general practitioner and will inform them of incidental findings.
• Upper respiratory tract infection (e.g. colds), within 6 weeks.
• Serious acute infections (such as hepatitis, pneumonia or pyelonephritis) in the previous 3 months.
• 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 unless

they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH >40 mIU/mL or the use of one or more of the following acceptable methods of contraception:
a) Surgical sterilization (e.g. bilateral tubal ligation, hysterectomy).
b) Hormonal contraception (implantable, patch, oral, injectable).

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:	Recruiting
Start date (anticipated):	21-02-2020
Enrollment:	78
Type:	Actual

Ethics review

Approved WMO Date:	05-02-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-11-2021
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
Other	NL201900308
CCMO	NL69765.042.19