The role of innate lymphoid cells in asthma and rhinovirus-induced asthma exacerbations

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Allergic conditions
Study type	Interventional

Summary

ID

NL-OMON40943

Source
ToetsingOnline

Brief title
RILCA

Condition

- Allergic conditions
- Viral infectious disorders
- Bronchial disorders (excl neoplasms)

Synonym
asthma, virus-induced asthma exacerbation

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: ERC advanced grant

Intervention

Keyword: asthma, asthma exacerbations, innate lymphoid cells, rhinovirus

Outcome measures

Primary outcome

Part 1

1. Determination of the different ILC populations in the lungs and peripheral blood of allergic and non-allergic asthma patients, both with high blood eosinophils and compare these to healthy non-allergic controls
2. Determination of the differences in innate cytokine production between bronchial epithelial cells from these groups, at baseline and after in vitro RV16 infection.
3. Study the interactions between ILCs and bronchial epithelial cells, DCs, B cells and eosinophils.

Part 2

1. Investigate the effects of a RV16-induced exacerbation in asthmatics and healthy subjects on the proportion of the different pulmonary and peripheral blood ILC populations, as well as their activation and cytokine production.
2. Determination of the differences in innate cytokine production between bronchial epithelial cells from these groups, at baseline and after experimental RV16 infection.

3. Study the interaction between bronchial epithelial cells obtained before and after experimental RV16 infection and ILCs.

Secondary outcome

Part 1

1. Other immunological parameters, such as BAL cellular influx (neutrophils, eosinophils, basophils, T cells, B cells, macrophages, NK cells) and inflammatory mediator production.
2. Asses if the ILC populations in the lungs correlate with BAL cellular influx, inflammatory mediator production, lung function parameters.
3. Assess oxidative stress and cyto-protective responses in sputum supernatant and sputum macrophages.

Part 2

1. Difference in maximum drop in FEV1, change in baseline morning or evening FEV1 on days 1-14 after RV16 challenge after RV16 infection between healthy and asthmatic subjects.
2. Effects on Asthma Control Diary (ACD) and Wisconsin Upper Respiratory Symptom Survey - 21 question version (WURSS-21).
3. Other immunological parameters, such as BAL cellular influx (neutrophils, eosinophils, basophils, T cells, B cells, macrophages, NK cells) and inflammatory mediator production.
4. Assess if the different ILC populations in the lungs after RV16 challenge

correlate with clinical parameters, such as the maximum drop in FEV1, change in baseline morning or evening FEV1 on days 1-14 after RV16 challenge, ACD and WURSS-21.

5. Detection of RV16 specific B cells.

6. Assess oxidative stress and cyto-protective responses in sputum supernatant and sputum macrophages.

Study description

Background summary

Asthma is a very heterogeneous disease and recent studies have come up with different phenotypes of asthma. Many patients with asthma frequently suffer from exacerbations, which are characterized by episodes of acute aggravation of their symptoms. The majority of asthma exacerbations have a viral etiology, rhinovirus being the most prominent pathogen. The mechanisms underlying these exacerbations are still not completely understood. We recently discovered of type 2 human innate lymphoid cells (ILC2s) capable of promptly producing high amounts of IL-5, IL-9 and IL-13 upon activation. Murine studies point to an essential role of these cells in asthma and asthma exacerbations, ILC2 may be the main initiating cells in type 2 responses in asthma and asthma exacerbations in humans. The activation of these cells is driven by IL-33, IL-25 and TSLP, which are mainly produced by bronchial epithelial cells.

Study objective

This study aims to determine whether the ILC populations differ in the lungs of different phenotypes of asthmatic patients and healthy subjects and how these cells are regulated by bronchial epithelial cells. Furthermore we want to study how this is affected by rhinovirus infection.

Study design

Part 1:
After screening the patients will have one visit were blood will be drawn and a bronchoscopy will be performed. During the bronchoscopy a lavage will be done, an epithelial brush and 6 biopsies will be taken.

Part 2:

After screening the participants will undergo 2 bronchoscopies. During the bronchoscopy a lavage will be done, an epithelial brush and 6 biopsies will be taken. This will be done 5 days before and 2 days after infection with RV16. Moreover blood will be drawn on day -5, 2, 14 and 6-8 weeks after RV16 and lung function tests will be done. OPtionally on day -1 and 6 a sputum induction will be performed.

Intervention

In part 2 all participants will undergo a RV16 infection.

Study burden and risks

Part 1:
2 visits, 2x blood sampling, 2x lung function tests and 1x bronchoscopy

Part 2:
6 visits, 5x blood sampling, 5x lung function tests and 2x bronchoscopy, 1x RV16 infection and during 3 weeks daily recording of common cold and asthma scores and their FEV1 in a diary.
2 optional visits for sputum collection.

The bronchoscopy, with a lavage, brushes and biopsies, is an invasive procedure that- even though lidocaine anesthesia is applied- can be unpleasant and can induce dry cough and a sore throat. The brushing of the airways and the biopsies can give rise to a superficial bleeding which usually stops rapidly.

The experimental infection with RV16 will induce common cold complaints, probably to a lesser extend in the healthy volunteers. RV16 infection can exacerbate the asthma complaints.

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

Asthmatic patients part 1:
Adult-onset eosinophilic asthma patients with a physician*s diagnosis of asthma that started after the age of 18.
Stable on asthma medication, no exacerbation or changes in asthma medication in the past 4 weeks.
Non-smoking, or ex-smoking (<10py) if the patient has at least 12% improvement in FEV1 after inhalation of 400 µg salbutamol.
Sputum eosinophilia >3%.
Atopic and non-atopic patients will be distinguished based on total serum IgE. Atopy will be defined as a serum IgE levels >= 100.;Asthmatic patients part 2:
Mild-moderate asthmatic patients will be selected using the following inclusion
Age between 18 - 50 years at the screening visit
History of episodic chest tightness and wheezing
Controlled 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 (PY)
Clinically stable, no exacerbations within the last 6 weeks prior to the study
Use of ICS at a stable dose-equivalent of <= 500mcg/day fluticasone propionate
Baseline FEV1 > 80% of predicted
Airway hyperresponsiveness, indicated by a positive acetyl-ß-methylcholine bromide (MeBr) challenge with PC20 < 9.8 mg/ml
Positive skin prick test (SPT) to one or more of the 12 common aeroallergen extracts, defined as a wheal with an average diameter of >3 mm;Control subjects:
Age between 18 - 65 years at the screening visit
Non-smoking or stopped smoking more than 12 months and <= 5 PY
Baseline FEV1 > 80% of predicted
MeBr challenge with PC20 > 9.8 mg/ml

Steroid-naïve or those participants who are currently not on corticosteroids and have not taken any corticosteroids by any dosing-routes within 8 weeks prior to the study
Negative history of pulmonary or any other relevant diseases

Exclusion criteria

For part 1 and 2:
Women who are pregnant, lactating or have a positive urine pregnancy test at visit 1
Participation in any clinical investigational drug treatment protocol within the preceding 30 days
Concomitant disease or condition which could interfere with the conduct of the study, or for which the treatment might interfere with the conduct of the study, or which would, in the opinion of the investigator, pose an unacceptable risk to the patient;Furthermore the following additional exclusion criteria will be used in part 2 of the study:
RV16 titre > 1:6 in serum, measured at visit 1
History of clinical significant hypotensive episodes or symptoms of fainting, dizziness, or light-headedness
Usage of high dose ICS (>500 µg/day to fluticasone or equivalent). Use of low or medium dose ICS (<=500 µg/day fluticasone or equivalent) with or without permitted controller medications e.g LABA, LTRA is allowed
Experience of an asthma exacerbation in the 12 weeks prior to visit 1 requiring management with systemic steroids
Has had any acute illness, including a common cold, within 4 weeks prior to visit 1
Ongoing use of tobacco products of any kind or previous usage with >= 6 total PY
Close contact with young children (< 2 years)
Has donated blood or has had a blood loss of more than 450 mL within 60 days prior to screening visit 1 or plans to donate blood during the study

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2015
Enrollment:	46
Type:	Actual

Ethics review

Approved WMO

Date:	09-04-2015
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

No registrations found.

In other registers

Register	ID
CCMO	NL48912.018.14
Other	NTR zal worden aangevraagd