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

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON45207

Source
ToetsingOnline

Brief title
RILCO

Condition

- Bronchial disorders (excl neoplasms)

Synonym
COPD virus-induced exacerbation

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: bedrijf MedImmune

Intervention

Keyword: COPD, COPD exacerbation, innate lymphoid cells, rhinovirus

Outcome measures

Primary outcome

Part 1

1. Investigate the effects of a RV16-induced exacerbation in COPD patients 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.

Part 2

1. Determination of the different ILC populations in the lungs and peripheral blood of COPD patients, who differ with respect in COPD severity, and compare these to healthy controls without COPD/asthma.

2. Study the interactions between ILCs and bronchial epithelial cells and other local cells.

Secondary outcome

Part 1

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

COPD patients.

2. Effects on two questionnaires for COPD symptoms (http://www.catestonline.org/english/indexEN.htm and as described in Mallia P, et al. Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. Am J Respir Crit Care Med. 2011 Mar 15;183(6):734-42).

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, and questionnaires.

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

Part 2

1. Asses T lymphocytes and NK cells in blood and lung tissue from patients and controls.

Study description

Background summary

COPD is a chronic lung inflammatory disorder defined by irreversible and progressive airflow obstruction. Severity of COPD ranges from mild to severe

(GOLD I - IV). Importantly, progression of this disease has been linked to exacerbation frequency. Acute exacerbations in COPD are typically associated with viral infections, predominantly rhinovirus. Frequent exacerbations not only accelerate disease, but impair quality of life, increase the risk of hospitalization and are the major cause of mortality and morbidity in these patients. The mechanisms underlying virus-induced exacerbations are still far from clear. Innate Lymphoid Cells (ILCs) represent a novel subset of immune cells that have recently been described to play critical roles in allergic asthma, helminth infections, colitis/IBD, anatomical containment of commensal bacteria, and tissue remodeling following injury or infection. Preliminary findings suggest that ILC2 and ILC3 populations are significantly reduced in COPD patients while there is a corresponding increase in the ILC1 subset. Human bronchial epithelial cells are the major cell type infected by RV in the lower respiratory tract in vivo and are capable of driving ILC plasticity.

Study objective

This study aims to determine whether the ILC populations differ in the lungs of COPD patients, who differ with respect to COPD severity, 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 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 -14, 2, 6, 14 and 6-8 weeks after RV16 and lung function tests will be done. On day -1 and 6 a sputum induction will be performed.

Part 2:
After screening blood will be drawn once just before or after lung resection.

Intervention

In part 1 all participants will undergo a RV16 infection.

Study burden and risks

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

The bronchoscopy, with a lavage, brushes and biopsies, is an invasive procedure that- even though lidocaine anaesthesia is applied- can be unpleasant and can induce dry cough and a sore throat. According to the standard operating procedure from Endoscopy a midazolam/propofol conscious sedation will be given to minimize discomfort. 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 COPD symptoms.

Part 2:
1x blood sampling

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

For rhinovirus challenges, patients
* non-smoking, or ex-smoking (*1 years ago), *10 pack years; GOLD stage II (post bronchodilator FEV1 <80% predicted and FEV1/FVC <70%)
* Allowed COPD specific medication: LABA and LAMA medication will be allowed, but no ICS
* Have no history of bronchiectasis, lung cancer or other significant respiratory disease.
* Be stable on COPD medication, no exacerbation or changes in COPD medication in the past 6 weeks. ;The age- and smoking history-matched controls will be extensively characterized with respect to lung function, medication and medical history. They have to:
* Be non-smoking, or ex-smoking (*1 years ago)
* Have no respiratory diagnosis of asthma or COPD
* Have no history of bronchiectasis, lung cancer or other significant respiratory disease.;For the COPD patients not challenged with rhinovirus:
* non-smoking, or ex-smoking (*2 years ago), GOLD I, II, IV
* no history of bronchiectasis, lung cancer or other significant respiratory disease;Non-COPD control group, not challenged with rhinovirus:
* Be non-smoking, or ex-smoking (*2 years ago), apart from those belonging to the controls who smoke
* Have no respiratory diagnosis of asthma or COPD

Exclusion criteria

For rhinovirus challenges,
* Women who are pregnant, lactating or have a positive urine pregnancy test at visit 1
* RV16 titre > 1:6 in serum, measured at visit 1
* Has had any acute illness, including a common cold, within 4 weeks prior to visit 1
* 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;For the patients not challenged with rhinovirus:
* 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

Study design

Design

Study type: Interventional
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-09-2015
Enrollment:	65
Type:	Actual

Ethics review

Approved WMO Date:	11-06-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2017
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

No registrations found.

In other registers

Register	ID
CCMO	NL52194.018.15
Other	NTR zal worden aangevraagd