Autoimmunity in Chronic Obstructive Pulmonary Disease

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON35095

Source
ToetsingOnline

Brief title
Autoimmunity in COPD

Condition

- Immune disorders NEC
- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
chronic bronchitis, COPD, emphysema

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Astma Fonds (binnenkort Long Fonds)

Intervention

Keyword: antibody, autoimmunity, COPD, cytotoxicity

Outcome measures

Primary outcome

The degree of autoantibody-mediated cytotoxicity of sera of COPD patients when compared to non-COPD patients, expressed as a fraction of cells that have died during incubation.

The cell types (primary bronchial epithelial cells, primary airway smooth muscle cells, primary lung fibroblasts) and cell lines (an alveolar epithelial cell line and a lung fibroblast cell line) that are primarily affected by autoantibodies as found in serum of COPD patients and healthy controls

The contribution of complement, different effector cells, and antibody-free serum to the level (as outlined in the previous paragraphs) and specificity of cytotoxicity (which cells and cell lines are affected). The impact of different effector cells and antibody-free serum.

Secondary outcome

Effects of age, aspects of smoking history, clinical and immunological parameters on cytotoxicity

Insight into the components which play a role in lung remodelling and destruction. We expect that results will lead to more attention for COPD and more focus on relevant targets in drug development programs.

A better understanding of the mechanisms underlying the pathological changes in lungs of patients with COPD, and identification of characteristics of patients which may benefit from anti-autoimmune therapy. This is necessary to be able to develop more targeted drug development programs and to develop efficient therapies.

Due to the similarities of COPD to other autoimmune disease (outlined above), opportunities for improved treatment and medication may in part be based on regimes used in other autoimmune diseases.

Study description

Background summary

Chronic Obstructive Pulmonary Disease or COPD is characterized by a temporally variable chronic bronchitis (infection of the lower respiratory tract) and emphysema. COPD gives rise to coughing, mucus production, and a distressing reduction of the oxygen carrying capacity of the lungs under physical exercise. Ultimately, the lack of oxygen intake will lead to death. In 2020, COPD will be death cause number three worldwide.

The cause of COPD is unknown, but smoking is the most important risk factor. The chronic inflammation in the lung associated with COPD can not be stopped and disease progression can not be slowed by currently available medication. As a consequence, further research is needed to improve treatments.

Recently, findings of high concentrations of B cells in lungs and various corollaries between COPD and other autoimmune diseases were noted. A postulated antigen-specificity is used here to identify cytotoxicity in sera of COPD patients and healhty participants. In addition, we will identify cellular targets of the autoantibodies in cell cultures and in primary tissue. If autoimmunity indeed operates, it is to be expected that sera of COPD patients and healthy controls differ in cytotoxicity and in specificity of the antibodies in terms of the cell types that are targeted.

Study objective

Our hypothesis is that antibodies of COPD patients contribute to inflammatory processes leading to cell death, and that the level of cytotoxicity differs between COPD patients and healthy volunteers.

The prime aim is to detect differences in antibody-mediated cytotoxicity in serum of COPD patients and healthy participants using an in-vitro based system encompassing target cells (cell lines, primary material), effector cells (PBMCs), and serum and to identify the lung cells that are most susceptible to antibody-mediated cytotoxicity.

Although most COPD patients exhibit features of autoimmunity, it is likely that the level of cytotoxicity varies form patient to patient. Consequently, also the level of self-reactivity and lung damage as well as the susceptibility of different types of lung cells to cytotoxic serum is likely to vary among groups of patients. Monitoring this variability in the COPD population is an important goal of this study.

We will also examine the cytotoxic effect of (heat inactivation of) complement, different effector populations, and antibody-free sera in this in-vitro system.

Study design

Antibody-mediated cytotoxicity in COPD patients and healthy volunteers will be studied by in-vitro assays, in which target cells, PBMCs, and serum are incubated, followed by a determination of cell death (here radioactive labeling). As target cells, we will use primary bronchial epithelial cells, primary airway smooth muscle cells, primary lung fibroblasts, an alveolar epithelial cell line (A549 cells), and a lung fibroblast cell line (MRC5). Lung primary cells are obtained from surgical resection material. Effector cells (PBMCs) from healthy donors are sampled and used freshly.

We will use serum from COPD patients (n=60) and smoking and non-smoking (n=60) healthy age-matched controls. Each serum sample will be used untreated (complement active) as well as complement-inactivated and as antibody-free serum. Also different effector populations will be tested (neutrophils, macrophages).

The level of cytotoxicity and the impact of complement (in)activation will all be studied by comparing cases and controls. For all participants, information on general health status and respiratory characteristics (spirometry, allergy) will be collected.

Study burden and risks

A small amount of blood will be donated by COPD patients and healthy controls.

This may cause localized bruising. For patients who have not yet been seen at the UMCG, a physical examination, a spirometry before and after bronchodilatation, and a skin test will be performed. For both patients and healthy participants, there are limited risks (haematoma resultin from the donation of blood and an irritated skin after the skin test). As this is an exploratory study, there are no direct benefits resulting from participation.

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

COPD patients:
• Clinical diagnosis of COPD
• No allergies
• Post-bronchodilator FEV1 < 80% predicted, and postbronchodilator FEV1/FVC<70%

• Age > 40
• Current or ex-smokers > 10 pack years
• Ex-smokers have to have quitted smoking for at least one year
• No other major current health problems
• Written informed consent;Healthy controls:
• No signs of pulmonary disease
• No allergies
• No other major current health problems
• FEV1 > 90 % predicted and FEV1/FVC > 70%
• Age > 40
• Never smokers, i.e. no cigarettes last year, and < 5 pack years, or current smokers > 10 pack years; or ex- smokers for > 1 year and > 10 pack years
• Written informed consent

Exclusion criteria

• Addiction to alcohol or drugs
• COPD exacerbation in the 6 weeks preceding the study

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:	Recruitment stopped
Start date (anticipated):	21-05-2010
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	22-04-2010
Application type:	First submission
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	Nederlands Trial Register, TC = 2259
CCMO	NL30449.042.10