Phenotype and number of regulatory T cells present in peripheral blood of COPD patients versus healthy controls

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Research questions:Is the chronic inflammatory response in COPD caused by a dysfunction of regulatory T cells?1. Is the number of Tregs decreased in COPD?2. Is the function of the Tregs impaired in COPD? And if so,a. Is this associated with a...

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

Summary

ID

NL-OMON30145

Source
ToetsingOnline

Brief title
Regulatory T cells 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: Ministerie van OC&W,Subsidie aangevraagd

bij Astmafonds;Stichting Astma Bestrijding en de Cock stichting

Intervention

Keyword: COPD, forkhead box P3 protein, Heme Oxygenase-1, Regulatory T-Cells

Outcome measures

Primary outcome

1. Treg numbers in peripheral blood of COPD patients vs healthy controls

2. Expression patterns of HO-1, TGFβ and Smad 7 in Tregs from COPD patients vs healthy controls

3. Functional capacity of Tregs from COPD patients vs healthy controls

4. Involvement of TGFβ signalling in suppresive function of Tregs from COPD patients vs healthy controls

Secondary outcome

1. Effects of smoking history on above described parameters

Study description

Background summary

COPD is a leading cause of death worldwide and its morbidity and mortality are still rising. Although the pathogenesis of the disease is still largely unknown, smoking is widely accepted as the most important cause for development of the disease. So far, no effective treatment is available to arrest the accelerated lung function loss associated with COPD, nor is there a cure. To find better treatment methods more insight is needed in the nature/origin of the chronic inflammation that underlies the development of COPD.
The important role of neutrophils, macrophages and cytotoxic T cells is well established in this respect, yet the role of CD4 T cells and B cells has only recently (re)attracted attention. We detected the presence of lymphoid follicles in lung tissue of COPD patients, consisting of B cells surrounded by T cells. Recently, we have found the presence of Foxp3 positive T cells as a component of these lymphoid follicles in COPD. Since Foxp3 is a distinctive marker of regulatory T cells (Tregs), this finding suggests that Tregs are

involved in the inflammatory response in COPD.
Tregs have been subject of investigation in allergy and asthma. They are important in controlling immunological tolerance and preventing auto-immune responses by inhibiting T-cell responses. Dysfunction of Tregs can lead to auto-immune diseases, allergy and chronic inflammatory diseases. However, nothing is known so far about their contribution to the chronic inflammatory response in COPD. The currently best described subset of Tregs is that of the naturally occurring Tregs. Naturally occurring Tregs are generated in the thymus and express CD4, CD25 and Foxp3. Recent studies show that, next to direct inhibition by cell-cell contact, the inhibitory effects of Tregs are mediated by heme oxygenase-1 (HO-1) expression and membrane bound TGFβ. We hypothesise that a dysfunction of regulatory T cells underlies the development of the (antigen driven) inflammatory response in COPD. This could be due to a decreased presence of Tregs in COPD, or to an altered function of Tregs. The latter may be due to a decreased HO-1 expression, as we have shown in macrophages of COPD patients compared to those in healthy controls, and/or an altered TGFβ regulation, a cytokine that plays a prime role in COPD.

Study objective

Research questions:
Is the chronic inflammatory response in COPD caused by a dysfunction of regulatory T cells?
1. Is the number of Tregs decreased in COPD?
2. Is the function of the Tregs impaired in COPD? And if so,
a. Is this associated with a decreased HO-1 expression?
b. Is this associated with an altered TGFβ regulation (e.g. by the signalling of SMAD7)?

Study design

Experiments:
1. Treg numbers and HO-1,TGFβ, Smad 7 and Foxp3 expression in COPD patients compared to controls
First it is important to investigate whether COPD patients have lower numbers of Tregs than healthy individuals and whether COPD patients have Tregs with an altered HO-1, TGFβ, Smad 7 or Foxp3 expression.
Numbers of Tregs (CD4, CD25, Foxp3) present in freshly isolated lymphocytes from peripheral blood from COPD patients will be analysed using flowcytometry and compared with age and smoking history matched healthy controls. In addition the expression of HO-1, TGFβ and Smad 7 will be analysed in these cells.

2. Treg function in COPD

To study the function of Tregs in COPD patients the inhibitory capacity of the Tregs will be investigated with proliferation assays and the cytokine

production will be measured.
CD4CD25high T cells will be freshly isolated from peripheral blood of COPD patients and healthy individuals and will be co-cultured with stimulated CD4CD25neg T cells (CD3/CD28). Proliferation of the CD4 T-cell population will be analyzed by 3H-thymidine incorporation and the cytokine production of these cells (IL-2, IL-10, and TGFβ) will be studied using ELISAs.

3. Involvement of TGFβ signalling

To investigate whether TGFβ signalling is involved in the suppressive effect of Tregs and is altered in COPD, the expression of Smad 2, 3 and 7 will be analysed.
CD4CD25high T cells will be freshly isolated from peripheral blood of COPD patients and healthy individuals and will be co-cultured with stimulated CD4 T cells (CD3/CD28). Intracellular expression of Smad 2, 3 and 7 will be analysed with flowcytometry in CD4 T cells and CD4CD25 Tregs after co-culture and in the single populations without co-culture.

Study burden and risks

Participants involved in this study are asked to visit the lung department of the UMCG two or three times.
At the first visit there will be a short interview with the physician to check their current health status, participants will perform spirometry to check for their lung function, and a skin test to check for allergies. In addition, they will be asked to fill in a Clinical COPD Questionnaire (CCQ). When a reversibility test is not necessary participants will also perform a methacholine provocation test to measure the hyperreactivity (PC20) and donate 20ml of peripheral blood for the flowcytometry experiments during the first visit. Healthy controls do not need a reversibility test for inclusion in the study and will perform a methacholine provocation test during the first visit.
COPD patients with a known FEV1 < 80% predicted and an FEV1/FVC < 70% measured during the last 5 years also do not need a reversibility test, but when this information is not present a reversibility test is required for inclusion and the methacholine provocation test has to be performed at a second visit.
At the second or third visit, participants are asked to donate 80ml of peripheral blood for experiments 2 and 3.

Risk for the participants in this study is are:
• Dyspnea during methacholine provocation test
• Irritated skin after skin test
• Haematoma from the donation of blood.
Participants have to stop using (inhaled) corticosteroids 6 weeks before visit 2 and 3, because this medication can influence the results of the study.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
9713 GZ
Nederland
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
9713 GZ
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

COPD patients
• Clinical diagnosed COPD
• FEV1 < 80% predicted, FEV1/FVC < 70%
• No use of (inhaled) corticosteroids in the 6 weeks preceding the study
• Age > 40
• > 10 pack years
• Ex-smokers have to have quitted smoking for at least one year
• No other health problems
• Informed consent;Healthy controls:
• No signs of pulmonary disease
• No other health problems
• FEV1 > 90 % predicted, FEV1/FVC > 70%

• Age > 40
• Smokers and ex- smokers > 10 pack years
• Never smokers, i.e. no cigarettes last year, and maximal 5 pack years
• Ex-smokers have to have quitted smoking for at least one year
• Informed consent

Exclusion criteria

• Use of (inhaled) corticosteroids in the 6 weeks preceding the study
• Problems with 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):	07-12-2006
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

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
CCMO	NL13036.042.06