Responsivity and reproducibility of messenger and micro RNA airway inflammatory markers - a pilot study

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Primary objectives: - Determination of the reproducibility and responsivity of mRNA levels of IL-6, IL-8, TNF-alpha, MCP-1, MIP-1 beta and TGF-beta as inflammatory markers in induced sputum- Determination of the reproducibility and responsivity of...

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

Summary

ID

NL-OMON50575

Source
ToetsingOnline

Brief title
mRNA and miRNA airway inflammatory markers - a pilot study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
COPD

Research involving
Human

Sponsors and support

Primary sponsor: Longziekten
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: airway inflammatory markers, COPD, reproducibility, responsivity

Outcome measures

Primary outcome

Primary endpoints of induced sputum samples:

The main parameters of induced sputum samples will be mRNA level expression of IL-6, IL-8, TNF-alpha, MCP-1, MIP-1 beta and TGF-beta.

Primary endpoints of nose mucosa samples:

The main parameters of nose mucosa samples will be mRNA and miRNA level expression of IL-6, IL-8, IL-17, TNF-alpha, MCP-1, MIP-1 beta and TGF-beta.

Therefore, three consecutive sputum inductions and nasal brush extractions will take place in a 7 week period.

The obtained data from Visit 1 and 2 will used to analyze the responsivity of these inflammatory markers during a marked change in inflammatory state. The obtained data from Visit 2 and 3 will be used for the analysis of reproducibility of these inflammatory markers.

Secondary outcome

The following parameters will be investigated for our secondary objectives in induced sputum of COPD patients:

- Inflammation cell profiles

- LTB4 levels

- protein levels of IL-6, IL-8, TNF-alpha, MCP-1, MIP-1 beta, ECP and

TGF-beta

Study description

Background summary

Progressive airway inflammation and remodelling represent the main underlying features in the pathogenesis of chronic obstructive pulmonary disease (COPD) (Wessler & Kirkpatrick, 2008). Changes of pulmonary function represent the mainstream outcome measure regarding the assessment of response to treatment in COPD in daily clinical practice, but it reflects only poorly the underlying pathology as well as the burden to the patient. Therefore, there is an increased interest to identify sensitive airway biomarkers in order to evaluate the potential and efficacy of anti-inflammatory and *remodelling therapeutic interventions (Singh, Edwards, Tal-Singer, & Rennard, 2010; Kistemaker, Oenema, Meurs, & Gosens, 2012).

Since the respiratory tract extends from the nose to the lungs, there are several procedures to analyse inflammatory processes of the airway mucosa, which might contribute to identify such airway biomarkers.

Because the inflammatory process among others leads to an accumulation of inflammatory mucous in the lumen, the analysis of sputum represents a non-invasive method, which allows the objective assessment of response to treatment and disease activity in the lower airways (Hogg et al., 2004). It has been repeatedly shown that COPD patients exhibit increased numbers of inflammatory cells, as well as increased concentrations of various inflammatory markers in induced sputum (O*Donnell et al., 2004; Rutgers et al., 2000; Singh et al., 2010). However, the reproducibility and responsivity of cytokine measurements in sputum exhibit a number of limitations. Several factors contribute to this, including the inability to cough up spontaneous sputum in some patients, variable dilution due to inducing sputum by nebulized saline solutions, variable concentration effects of treatment such as anticholinergics, and the dissolution of disulfide bridges in many cytokine proteins upon DTT pretreatment needed to dissolve the sticky sputum. These problems have provided a major contribution to two studies failing to demonstrate consistent associations between reduction of COPD exacerbations and cytokine concentrations in induced sputum of patients who were treated with anticholinergics (Powrie et al., 2007; Perng et al., 2009). In both studies methodological problems in the determination of protein levels and in variable dilution were a major drawback.

It has been shown that airway inflammatory responses can be found at different airway epithelial sites, including the nasal mucosa. It has been shown that cytokine responses in the nasal epithelium might be used as suitable surrogate for epithelial cells of the lower airways in patients with airway inflammatory diseases (Comer, Elborn, & Ennis, 2012; Huang et al., 2016; Zhang et al., 2010). However, scientific knowledge is still limited regarding the relationship of cytokine gene expression between nasal and lower airway epithelium and requires further studies for validation.

In the light of prospective COPD interventional studies it is necessary to identify first stable airway biomarkers that overcome microbiological limitations of measuring cytokine concentrations in order to study possible anti-inflammatory and *remodelling effects of therapeutic interventions, later on. A promising approach is the analysis of m (messenger) RNA as an inflammatory marker. To our knowledge, there is only little data regarding the analysis of cytokine mRNA expression induced sputum as well as nasal epithelium in COPD patients. Even less information is available regarding mi (micro) RNA.

We aim to investigate cytokine mRNA and miRNA levels of IL-6, IL-8, IL-17, TNF-alpha, MCP-1, MIP-1 beta, ECP and TGF-beta expression regarding their reproducibility and responsivity in induced sputum and nasal mucosa in COPD patients in order to assess their potential as an objective outcome measure.

Study objective

Primary objectives:
- Determination of the reproducibility and responsivity of mRNA levels of IL-6, IL-8, TNF-alpha, MCP-1, MIP-1 beta and TGF-beta as inflammatory markers in induced sputum

- Determination of the reproducibility and responsivity of mRNA and miRNA levels of IL-6, IL-8, IL-17, TNF-alpha, MCP-1, MIP-1 beta and TGF-beta as inflammatory markers in nasal epithelium.

Secondary objectives:
Analyzes of the measurement characteristics of inflammation cell profiles, LTB4 and protein levels of IL-6, IL-8, TNF-alpha, MCP-1, MIP-1 beta, ECP and TGF-beta in induced sputum.

Study design

This is a prospective pilot study that will be conducted across seven weeks. Subjects with an initial COPD exacerbation will be recruited and followed for seven weeks. At three moments (3-4 days after the start of acute COPD

exacerbation, after 42 days and after 44-51 days) sputum as well as nasal mucosa samples will be collected by sputum induction, as well as nasal brushes, respectively.

Study burden and risks

Burden and risk associated with participation:
Sputum induction includes the inhalation of nebulised sterile hypertonic saline solution and can lead to transient bronchoconstriction. This can lead to coughing and shortness of breath. Participants will be previously informed about the potential side effect and pretreated with inhaled salbutamol and monitored during the process of sputum induction.

Nasal swab collections have the potential to irritate the intranasal cavity and lead to acute epistaxis; however the risks associated with discomforts from such events are minimal.

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

- Age >40 years at recruitment
- COPD patients with an FEV1/FVC < 0.7
- Diagnosis of moderate or severe COPD exacerbation
- FEV1 > 0.8 L and ability to produce sputum after hypertonic saline production
- A smoking history of >10 pack years

Exclusion criteria

- Acute pneumonia as determined by X-ray
- > 48 h intake of prednisolon/antibiotics
- Need for mechanical ventilation (either invasive or non-invasive)
- Treatment with immune-modulating agents for any disease
- Experimental interventions for COPD last half year
- Former/concomitant diagnosis of asthma
- Any significant other pulmonary disease or disorder
- Existing pregnancy/ current willingness for becoming pregnant

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-04-2018
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	14-11-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-06-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-03-2020
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
CCMO	NL62038.042.17