Pilot study: Biomarkers for the diagnosis of severe neutrophil inflammatory asthma.

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The aim of this pilot study is to validate potential biomarkers which diagnose patients who will benefit from asthma treatment with macrolide therapy by using non-invasively collected body fluid specimens. Th1/Th2/Th17 patterns in patients suffering...

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

Summary

ID

NL-OMON42933

Source
ToetsingOnline

Brief title
Biomarkers for severe neutrophil inflammatory asthma

Condition

- Allergic conditions

Synonym
Severe asthma

Research involving
Human

Sponsors and support

Primary sponsor: Rijnstate Ziekenhuis
Source(s) of monetary or material Support: - Vriendenfonds Rijnstate;- Wageningen Universiteit

Intervention

Keyword: Biomarkers, Neutrophils, Severe asthma

Outcome measures

Primary outcome

Th1/Th2/Th17 patterns by analysing cytokine concentrations (Th1: IL-2, TNF,

IFNγ; Th2: IL-4, IL-6, IL-10; Th17: IL-17A) in nasal fluid (nasal wash and

cotton wool method), saliva and blood.

Secondary outcome

n.a.

Study description

Background summary

About 10% of all asthmatics have difficult-to-treat/refractory asthma (=severe asthma), which is characterised by uncontrolled asthma, even when high doses of inhaled corticosteroids and a second controller are administered. Severe asthma is associated with increased neutrophils and T helper (Th) 17 chemokine overexpression in bronchial biopsies.
Phenotyping of patients is important to optimize therapy and disease outcome. Whereas eosinophilic asthma patients respond well to anti-inflammatory treatment with steroids, severe eosinophilic and non-eosinophilic asthma patients (including neutrophilic asthma patients) show inadequate response. For non-eosinophilic/non-allergic (neutrophilic) asthma therapeutic options are focused on targeting the Th17/IL-17 route.; i.e. treatment with macrolide antibiotics. For severe eosinophilic (with or without allergy) anti-IL-5 or anti-IgE might be therapeutic options.
In the Netherlands, asthma affects up to 3.5% of the adults and 4% of the children below the age of 15 yrs. In 2007 the overall health expenditure was ¤ 300 million. Half of these costs involve medication, i.e. combination preparations (a long-acting-sympathomimetic agent with inhaled corticosteroids). The annual direct medical expenditures and indirect nonmedical costs range from around ¤500 for controlled asthma to ¤2281 for uncontrolled asthma.
Since severe asthma burdens on overall health costs, early phenotypic classification of severe asthma can guide the choice of the most appropriate

therapy with a reduction of exacerbations and health costs.
Until recently, cell analysis in sputum induction was used for asthma phenotyping. However, this is an expensive technique, not widely available and is uncomfortable for the patient. For eosinophilic/allergic asthma non-invasive diagnostic test are available; e.g. blood eosinophils, serum IgE/Skin Prick Test, exhaled nitric oxide. However, routine non-invasive laboratory tests are not available for the diagnosis of patients with neutrophilic asthma. Furthermore, it is unknown which patients with non-eosinophilic/non-allergic asthma will respond well to macrolide therapy. Asthma is more and more considered to be an inflammatory disease of both the lower and upper airways. This is also reflected in multiple publications showing a significant correlation between the cytokine profiles in induced sputum/bronchial biopsy and nasal biopsy, showing that the nose may be considered the window of bronchi in asthma. A recent study by Sorbello et al. (2015) showed for uncontrolled/severe asthma, in contrast to mild asthma and controls, increased neutrophils/IL-17 in nasal/bronchial biopsies. Furthermore, significant correlations were observed between bronchial IL-17 and neutrophils, nasal IL-17 and bronchial neutrophil/IL-17, suggesting that nasal IL-17 might be informative on bronchial IL-17-driven neutrophilia. Albano et al (2013) showed that levels of IL-17 were higher in induced sputum and nasal lavage of children with mild-moderate astma compared to intermittent asthma and healthy controls. Little et al. (2014) showed that even saliva might be suitable for phenotyping patients with asthma since salivary myeloid markers (like IL-8) were associated with disease control and exacerbations. As nasal lavage and saliva collection are less invasive procedures compared to sputum induction, these body fluids are of particular interest for further research.

Study objective

The aim of this pilot study is to validate potential biomarkers which diagnose patients who will benefit from asthma treatment with macrolide therapy by using non-invasively collected body fluid specimens. Th1/Th2/Th17 patterns in patients suffering from severe eosinophilic and/or allergic asthma and non-eosinophilic/non-allergic asthma are compared. The group of non-eosinophilic/non-allergic asthma patients will be tested twice, before and after treatment with macrolide therapy during 12 weeks (standard therapeutic procedure). Th1/Th2/Th17 patterns are determined by analysing cytokine concentrations (Th1: IL-2, TNF, IFNγ; Th2: IL-4, IL-6, IL-10; Th17: IL-17A) in nasal fluid (nasal wash and cotton wool method), saliva and blood. The results of these factors in the asthma subpopulations will also be compared to the results found in the pilot study with healthy controls. The pilot study with healthy controls (METC nr NL56960.091.16) was conducted recently.

Study design

The study is an observational pilot study with restricted invasive treatment.

The study involves 20 patients suffering from severe eosinophilic and/or allergic asthma, and 20 patients suffering from severe non-eosinophilic/non-allergic asthma (eligible for macrolide therapy). The group of non-eosinophilic/non-allergic asthma patients will be tested twice, before and after treatment with macrolide therapy during 12 weeks. All patients are 18 years or older and mentally competent. Subjects will visit the department of pulmonary medicine of the Rijnstate Hospital in Arnhem. The visit will take 30 to 45 minutes. During the visit blood, nasal fluid (two different methods) and saliva (one tube per fluid per time) will be collected. The fluids will be processed and stored until analysis of the Th1/Th2/Th17 patterns. In addition, C-reactive protein (CRP) will be measured in the blood to exclude an acute phase and total protein in nasal fluid and saliva will be measured to express cytokine levels on the total protein content.

Study burden and risks

Subjects have to donate a small amount of nasal fluid, saliva and blood in a certified hospital environment (KHCL Rijnstate Arnhem). Risks of participation include the regular risks involved in the sampling procedures; i.e. pain and bruises (for blood sampling), irritation and a dry feeling in the nose (for the collection of nasal fluid).

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

All patients included in this study suffer from severe asthma. When a diagnosis of asthma is confirmed and comorbidities have been addressed, severe asthma is defined as asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic CS) to prevent it from becoming *uncontrolled* or which remains *uncontrolled* despite this therapy.

Exclusion criteria

-People suffering from other (chronic, pulmonary or autoimmune) diseases than asthma
-People suffering from an upper or lower respiratory infection within four weeks prior to investigation
-People having an immunodeficiency
-People taking antibiotics (macrolide trial included) or probiotics, four weeks prior to investigation
-People taking oral corticosteroids
-People who smoke.

Study design

Design

Study type:	Observational invasive
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):	14-07-2017
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO

Date:	22-02-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL57426.091.16