Pharmacogenetics of Asthma Medication in Children: Medication with Anti-inflammatory effects with special focus on Neutrophils.

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

Summary

ID

NL-OMON41390

Source
ToetsingOnline

Brief title
Pacman-cohort

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Asthma

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Utrecht

Source(s) of monetary or material Support: Ministerie van OC&W,GlaxoSmithKline,Universiteit Utrecht-GSK : strategische alliantie (voor PACMAN1).

Intervention

Keyword: asthma, children, pharmacogenetics, treatment response

Outcome measures

Primary outcome

Study outcome:

- treatment response.

- biomarkers for therapy response

Study parameters:

- genetic polymorphisms (SNPs)

- patient characteristics (other than genetic factors)

We will focus on SNPs in genes involved in pharmacological asthma treatment pathways. To measure the treatment response and to make correctuin for confounders the parents are asked to fill in a questionnaire on symptoms, medication use, environmental factors etc. In addition we will assess whether we can measure the gut microbiome in children who remain uncontrolled despite treatment in a pilot study setting.

Secondary outcome

Not applicable

Study description

Background summary

Asthma is a chronic inflammatory airway disease, which is characterised physiologically by recurrent airway obstruction that resolves spontaneously or as a result of treatment. Asthma is the most common chronic disease in children. Although the etiology of asthma is still not fully clear, there are effective treatments for asthma. Standard treatment is based on regular use of inhaled corticosteroids in combination with ß2-agonists, to prevent asthma exacerbations, retain proper lung function and modulate inflammatory responses. However, not all patients respond similarly and there is a huge variation in individual responses to therapy. The response of an individual patient to a given drug depends on a range of factors, including compliance, comorbidity, disease severity, environmental factors and genetic background. Polymorphisms in the genes encoding relevant anti-asthma drug targets can contribute significantly to this variability.
Pharmacogenetics, focusus on the question of the extent to which the expression of genetic background is responsible for interindividual variablity in drug response. Earlier studies on asthma pharmacogenomics have primarily focussed on adult patients. In this study, pharmacogenetics of asthma medication will be studied in children for two reasons: (i) Asthma is the most common chronic disease in childhood and (ii) in children treatment response is not biased by years of medication use and environmental factors such as smoking.

In the second phase of this study we will focus on inflammatory patterns in asthma and we aim to identify non-genetic markers for therapy response, with a focus on inflammatory markers. Airway inflammation is an important hallmark of asthma. Inflammation in asthma is often described as being 'eosinophilic' based on the increased presence of primed eosinophils in the airways, though inflammation in asthmatics may also occur in the absence of eosinophils. Different types of immune cells are known to respond differently upon asthma medication in vitro. More knowledge on the different patterns of inflammation in asthma and the relation with therapy response, may lead to the identification of predictive inflammatory biomarkers and an improved treatment of asthmatic patients.

In addition, we are interested in microbiome biomarkers. The microbiome contains a novel pool of asthma biomarkers. These markers can be obtained non-invasively, which is important for children.

Study objective

The overall aim of the project is to define effects of genetic and non-genetic variants on pharmacological treatment response in children with asthma.

The following questions will be answered:
- What are the characteristics of children who do not respond to pharmacological treatment?
- Which polymorphisms in genes involved in pharmacological or anti-inflammatory pathways can be detected?
- Which polymorphisms in genes involved in pharmacological or anti-inflammatory pathways are associated with treatment response?
- Do children who do not respond to asthma medication have a different type of airway inflammation than children who respond well to asthma medication?
- are there inflammatory biomarkers that can predict therapy response in pediatric asthma medication users?
- can we measure the microbiome in children with uncontrolled asthma despite treatment?

Pharmacogenomics, as well as proteomics and immunophenotyping, will give tools to characterise and predict treatment response in children with asthma.

Study design

The study exists of an invitation of child/parents for interview & inhalation instruction and DNA collection (saliva sample) and genotyping. During the visit in the pharmacy, we will also measure the child*s lung function (FVC and FEV1) with the help of a hand-held diagnostic spirometer (EasyOne). In this way, simple assessment of lung health is possible in the office setting. This kind of spirometer meets ATS (American Thoracic Society) recommendation for diagnostic spirometry. In addition, we will also measure NO (nitrix oxide) in expiration air with a hand-held analyzer (Niox Mino). This is an easy to use tool for monitoring (airway) inflammation in asthma patients.A letter to the GP will be sent to collect additional health information on the children. We will ask the GP if the child is diagnosed with asthma (yes/no/uncertain) and we will also ask if there is information from the past 12 months on IgE (in blood) and lung function tests (spirometry and bronchial hyperresponsiveness).

In phase 2 of this study we will invite a subpopulation for an additional visit to the Wilhelmina Children's Hospital to perform additional testing. We will invite children who show good adherence to inhaled corticosteroids, are 8 years or older and whose parents have given consent to be approached for future research during phase 1. In addition, we will recruit 10 patients with asthma (comparable to the non-responders) through the department of Pediatric Respiratory Medicine. The measurements during this additional visit include: lung function testing, a questionnaire on asthma for parent and child (digital, can be performed at home, in advance), measurement volatile and non-volatile compounds in expiration air, collection of a saliva sample and a venapunction will be performed (once, 30mL), in order to study inflammatory markers. Profiles of biomarkers will be compared between poor and good responders (who will be further stratified on NO levels). It is expected that approximately 180 children will be invited for phase 2 (see study protocol p.17).

We will ask the parents of the 5 last children to be included in the WKZ to collect a feces sample of their child at home (using an Oragene feces kit) and complete a questionnaire regarding factors of influence on the microbiome development (e.g. antibiotics use, way of birth and food intake). These measurements are non-invasive.

Study burden and risks

There are no risks associated with participation to this study. Patients are invited to for an interview, an inhalation instruction and two short lung function tests in the pharmacy. Furthermore, the patients are asked to donate a saliva sample.

Concerning phase 2 of the study; risks for the participants are minmial. A subset of the children will be invited for an additional visit to the Wilhelmina Children's Hospital to perform additional testing. The measurements of this additional examination include: lung function testing, a questionnaire on asthma for parent and child (to be filled in, in advance at home using the asthma portal), measurement of volatile and non-volatile compounds in expiration air, and the collection of a saliva sample; these measurements are non-invasive. Furthermore, blood will be drawn (once, 30 mL). Local anaesthetic creme or spray will be used to minimize the experience of pain during venapunction.

Concerning the microbiome measurements there are no risks associated with participation to this study. The measurements (questionnaire and feces samples collection) are non-invasive and can be performed at home.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- Use R03 drugs
- Age between 4-12 years
- Parents able to speak, read and write Dutch language
- At least 2 years of medication history available in which the child filled >=1 prescriptions for any asthma drug (RO3) within the last 6 months and at least 2 prescriptions in the last 12-24 months;For PACMAN phase 2 we will select a subgroup of these patients;
- parents consented to be approached for future research
- child is 8 years or older
- child is adherent to ICS
- child is classified as a non-responder (case) or responder to asthma medication (control)

Exclusion criteria

- child is younger than 8 years
- child does not use ICS
- child is not adherent to ICS
- consent is not obtained to be approached for future research during phase 1

Study design

Design

Study type: Observational invasive

Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-04-2009
Enrollment:	1010
Type:	Actual

Ethics review

Approved WMO Date:	11-11-2008
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-04-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-04-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL21242.041.08