A multicenter Longitudinal Study for Disease Profiling of Asthma

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This study is designed to identify molecular and cellular profiles in peripheral blood, urine, induced sputum, and bronchial tissue from three main categories of asthma (persistent mild, moderate and severe) and to correlate these profiles to...

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

Summary

ID

NL-OMON36306

Source
ToetsingOnline

Brief title
Disease profiling asthma

Condition

- Bronchial disorders (excl neoplasms)

Synonym
niet aanwezig

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag International NV;in NL vertegenwoordigd door Janssen-Cilag B.V.

Intervention

Keyword: asthma, disease, profiling

Outcome measures

Primary outcome

Biomarker assessments will include the evaluation of biomarkers in serum, urine, and whole blood as well as from endobronchial biopsy, brushings and induced sputum specimens. Potential markers include but are not limited to TNF*, IL-8, eotaxin, myeloperoxidase, MMP2, MMP9, IL-4, IL-13, cysteinyl leukotrienes, 8-isoprostane, mRNA and miRNA differential expression profiles.

Secondary outcome

genomic evaluation (if sucject consents for this part of the study)

asthma questionnaires

safety evaluations

Study description

Background summary

Airway inflammation, intermittent airflow obstruction, and bronchial hyperresponsiveness represent major components of asthma pathophysiology (Barnes, 2008; Linzer, 2007; Maddox and Schwartz, 2002). It has been proposed that an underlying cause of these components is inflammation that can be acute, subacute, or chronic (NIH, 1997; Toews, 2001). In addition, airway edema (Chu et al, 2001; Rogers and Evans, 1992) and mucus secretion (Rogers, 2004) also contribute to airflow obstruction and bronchial reactivity. Chronic airway inflammation leads to airway remodeling as characterized by subendothelial fibrosis, goblet cell hyperplasia, smooth muscle hypertrophy, thickening of basement membrane, and inflammatory cell infiltration (Maddox and Schwartz, 2002; Tidden et al, 2000). Also, increased epithelial shedding into the bronchial lumen (Yoshihara et al, 2006) could lead to exposure of sensory nerve endings and an imbalance in cholinergic and peptidergic neuronal control contributing to persistent airway obstruction.

The molecular and cellular mechanisms leading to airway inflammation as a response to different environmental triggers are not yet well understood although significant progress has been made. Some of the principal cells identified in airway inflammation include mast cells, neutrophils, eosinophils, epithelial cells, macrophages, and activated T lymphocytes. Numerous cytokines released by T lymphocytes play an important role in the regulation of airway inflammation. In addition, other airway cells such as fibroblasts, endothelial cells, and epithelial cells also contribute to the chronicity and severity of the disease (Yoshihara et al, 2006). On the molecular level, pro-inflammatory cytokines and other factors such as adhesion molecules (eg, selectins, integrins), lipid mediators (prostaglandins and leukotrienes) (Huang and Peters-Golden, 2008), oxygen radicals, and toxic granule proteins are critical in directing the inflammatory changes in the airway. Finally, cell-derived mediators influence smooth muscle tone and produce structural changes and remodeling of the airway (Barnes, 2008; Tiddens et al, 2000).
Lack of well defined markers for different disease phenotypes has been one of the main obstacles in understanding the natural progression of asthma and implementing the most adequate treatment. Recent studies (Woodruff et al, 2007; Woodruff et al, 2009) identified subsets of asthma patients with respect to the molecular mechanisms underlying airway inflammation. In these studies, messenger ribonucleic acid (mRNA) microarray expression profiles were obtained from airway epithelial cells (obtained by bronchoscopy/epithelial brushings) of 42 mild to moderate steroid-naïve asthma subjects and 28 healthy non-smoking control subjects. It was found that these asthma subjects had an increased expression of CLCA1, periostin, ovalbumin and serpinB2, compared to healthy controls (Woodruff et al, 2007), and that the mRNA expression levels of these genes could predict responsiveness to inhaled corticosteroids (Woodruff et al, 2007). The identified genes are highly regulated by IL-13 in cultured airway epithelial cells (Woodruff et al, 2009). In addition, the data suggested that asthma subjects could be divided into at least 2 distinct phenotypes (Th2-low and Th2-high) depending on the level of T helper lymphocyte 2 (Th2) inflammation as assessed by the expression level of IL 13 (Woodruff et al, 2009). The Th2-low asthma subgroup did not reveal any additional clustering suggesting that in at least 50% of asthma subjects other processes not related to Th2 may contribute to asthma phenotypes.

Study objective

This study is designed to identify molecular and cellular profiles in peripheral blood, urine, induced sputum, and bronchial tissue from three main categories of asthma (persistent mild, moderate and severe) and to correlate these profiles to respective clinical phenotypes.

Study design

This is a multi-center, longitudinal, exploratory study of biomarkers, clinical

and physiological parameters in subjects with mild, moderate, severe asthma and healthy control subjects. There is no therapeutic intervention and this protocol will not restrict or introduce any medical interventions including medications. Study participants will undergo procedures that include pulmonary function testing, assessment of airway reactivity, collection of blood samples for routine laboratory tests, biomarkers and DNA evaluation (in further consenting subjects), induced sputum collection, and exhaled nitric oxide collection. All subjects with asthma will have additional follow-up visits at 3, 6, and 12 months for repeat sample collection for biomarker analysis and the assessment of clinical and physiological parameters. Up to thirty subjects from each asthma severity group and all healthy subjects will undergo a bronchoscopy for collection of endobronchial biopsy and brushing samples. These samples will be used for analysis of proteins, RNA and other biomarkers in endobronchial tissue and epithelial cells.

Study burden and risks

The following risks are associated with trial participation and are mentioned in the information for the participant

Side effects from testing
• Blood tests: Taking blood may cause bruising at the place where the needle goes into the skin, fainting, and in rare cases infection.
• Lung Function Tests: Lung function testing may cause lightheadedness, dizziness, fatigue, coughing, or shortness of breath. You may experience some general chest discomfort from the deep breaths required to perform this test effectively. If you are concerned at any time during the test, you should inform the technician who is performing the test.
• Bronchodilator response test: Cases of hives, swelling under the skin, rash, tightening of muscles surrounding the airways, hoarseness, and irregular heartbeat havehas been reported after using albuterol/salbutamol. In addition, albuterol/salbutamol can cause adverse reactions such as increased blood pressure, chest pain, spinning sensation, central nervous system stimulation, sleeplessness, headache, and drying or irritation of the mouth and throat.
• Methacholine test: The methacholine test may cause headache, throat irritation, lightheadedness and itching and the same side effects as lung function testing. Also, as the test is designed to cause bronchospasm (narrowing of the airways), you will probably experience asthma symptoms such as wheezing, shortness of breath, and chest tightness. In rare cases, the test can cause severe bronchospasm. After the test or if the bronchospasm is severe, the technician will give you the medication to inhale that will open your airways.
• Induced Sputum Collection: You will be asked to breathe a mist of salt water through a mask for about 10 minutes. On several occasions, you will be asked to spit out your saliva and then to cough up mucus from your lungs into a sample pot. Sputum induction and the need to cough can cause shortness of breath in some patients, which is mild in most cases but can also be severe. Your lung

function will be measured before, during and after sputum induction and if shortness of breath occurs, the test may be stopped and you may be given treatment with medication that will open your airways or oxygen if these are necessary.
• Bronchoscopy: Fiberoptic bronchoscopy is a generally safe procedure with little risk of serious complications. The procedure however can cause serious complications although this is rare. Such complications are described below. Risks associated with bronchoscopy include the following:
• Side effects from the lung function tests performed before and after the procedure. These include lightheadedness, dizziness, fatigue, coughing, or shortness of breath. You may experience some general chest discomfort form the deep breaths required to perform the test effectively.
• Side effects from the medications used to cause sedation and to numb the airways. These include excessive sedation (sleepiness) and drowsiness after the procedure, allergic reactions to the medications and lidocaine toxicity from the numbing medications. Your doctor will ask you about medication allergy and will monitor you for signs of excessive sedation. The total dose of numbing medication will also be monitored to prevent toxicity.
• Nose or mouth bleeds due to the passage of the bronchoscope through the nasal passages or mouth. In rare cases, this bleeding may be severe.
• Bronchospasm of your airways: this may occur when the bronchoscope is passed into your airways and may cause you to wheeze, and experience shortness of breath and chest tightness like an asthma attack. If this happens, the bronchoscope may be removed, and you will be treated with the medication to relax your airways and given oxygen. The bronchspasm usually resolves quickly. In rare cases, the bronchspasm may be severe and prolonged and may result in the need to keep you in a medical facility overnight or even to be hospitalized.
• Mild bleeding from the airways is very common during bronchoscopy. You may notice some blood in your phlegm (mucus) after the test. In rare cases, bleeding can be severe and even life threatening.
• Pneumothorax. This is when air escapes due to puncture of your lung during the bronchoscopy and can cause collapse of the lung. This complication is less common after the planned procedures for the bronchoscopies (airway biopsies and brushings) during this study but could still occur. If a pneumothrax occurs, you may experience chest pain and shortness of breath. If your doctor suspects a pneumothorax, he or she may order a chest X-ray. A pneumothorax may require removal of the air by passing a needle or a tube into the chest wall, and/or hospitalization.
• Coughing during the procedure and after the procedure. This usually resolves quickly once the bronchoscopy is over.
• Infection of your lungs: bronchitis or pneumonia can occur in the first days or even a week after bronchoscopy. If this occurs you would notice a fever and you would cough up green sputum. If this happens you will need to be treated with antibiotics and could even need to be admitted to the hospital for treatment.
• Fever: some patients get a low grade temperature after bronchoscopy and this can last for up to a day.

• You may have a sore throat or hoarseness after the procedure. These symptoms are usually mild and improve quickly.
• Other risks include chills, muscle pain, decreased blood oxygen, and in rare cases death.
All of these risks are minimized having the procedure performed only by physicians who are experts in bronchoscopy, by having trained personnel assisting with the procedure, and by monitoring oxygen levels (using a finger clip) and heart rate (ECG monitoring) during the procedure. Facilities for the treatment of all emergencies are available, if needed.
Lidocaine is the medicine used to numb your throat and airways for the bronchoscopy procedure. If too much lidocaine is given to you, it can cause problems with your heart or blood vessels (slow heart beat, low blood pressure, or other changes to your heart rhythm), your breathing (overbreathing, shortness of breath, reduced oxygen in your tissues, or periods of time with reduced breathing), or your central nervous system (lightheadedness, dizziness, numbness, confusion, convulsions, unconsciousness, or coma). Because of this, the amount of lidocaine that is given to you, you will be carefully monitored to ensure that you do not get too much. Guidelines are in place to limit the dose of this medication, and a physician will be present until the effects of these medications have worn off.
If you receive additional sedation, it may diminish your recollection of the bronchoscopy procedure. Some people develop drowsiness, fatigue, headaches, a loss of coordination, nausea/vomiting, allergy to the medication, slow/shallow breathing, low blood pressure, nervousness, irritability, vein inflammation, and discomfort at the injection site. Your breathing will be continuously monitored, and if necessary, you will be treated for these reactions.
Additionally because these medications may make you drowsy, you must not plan to operate machinery or drive a motor vehicle until the next day. You will make arrangements for an adult to escort you home after this procedure.
There might be other discomforts or risks to you from this study that are not yet known. It might be that during the study [insert local legal entity company name] or your study doctor may learn new facts about bronchoscopy. It is possible that this information might make you change your mind about being in the study. If new information is discovered, your study doctor will tell you about it right away.
• Other procedures: physical examinations, blood pressure measurements, alcohol breath test, weight and height measurements, electrocardiogram are generally of no risk to you.

During the study your asthma condition may remain the same or get worse.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Healthy Subjects
Inclusion Criteria
Subjects must satisfy all of the following criteria to be enrolled in the study:
• Must have signed an informed consent indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
• Be willing and able to adhere to the study visit schedule and other protocol requirements.
• Be between 18 and 55 years of age, inclusive, at informed consent.
• Have no clinically significant abnormalities as determined by medical history, physical examination, blood chemistry assessments, hematologic assessments including complete blood count (CBC), urinalysis (see Attachment 2 for clinical laboratory analyses), measurement of vital signs, and ECG.
• Have a body mass index (BMI) of less or equal to 32* kg/m2.
• Must be able to produce an adequate induced sputum sample at screening, defined as a selected plug weight of at least 50 mg and a squamous cell count of < 20% (see Study Reference Manual).
• Must be judged by the Principal Investigator (PI) to be a subject suitable to undergo

bronchoscopy.
• Have no history of chronic respiratory disease including asthma.
• Have no history of allergic symptoms eg, allergic rhinitis, eczema.
• Be a non-smoker for >= 1 year at initial screening visit and have <= 10 pack- year history of smoking.
• No other acute illness in the 6 weeks prior to screening.
• No contraindications to the procedures in this study including clinical or research bronchoscopy.
• No bleeding disorder including use of anticoagulants and antiplatelet agents that could place the subjects at risk for bleeding. Able to abstain from aspirin use for 7 days and NSAID use for 3 daysprior to bronchoscopy without risk.
• No contraindications to conscious sedation or medications used in the bronchoscopy procedure.
• To participate in the optional genomic component of this study, subjects must have signed the informed consent for genomic research indicating willingness to participate in the genomic component of the study. Refusal to give consent for this component does not exclude a subject from participation in the study.;Subjects with Asthma
Inclusion Criteria for Asthmatic Subjects
Subjects must satisfy all of the following criteria to be enrolled in the study:
• Must have signed an informed consent indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
• Be willing and able to adhere to the study visit schedule and other protocol requirements.
• Be between 18 and 70 years of age, inclusive, at informed consent. Subjects who elect to undergo bronchoscopy must be between 18 and 55 years old, inclusive, at informed consent.
• Have no clinically significant abnormalities as determined by medical history, physical examination, blood chemistry assessments, hematologic assessments including CBC, urinalysis (see Attachment 2 for clinical laboratory analyses), measurement of vital signs, and ECG.
• Have a BMI less then or equal to 32 kg/m2.
• Must be able to produce an adequate induced sputum sample at screening, defined as a selected plug weight of at least 50 mg and a squamous cell count of < 20% (see Study Reference Manual).
• Be a non-smoker for >= 1 year prior to screening and have <= 10 pack- year history of smoking.
• No contraindications to the procedures in this study.
• Symptoms compatible with asthma for at least 6 months prior to screening (wheezing, dyspnea, chest tightness), PI confirmation of diagnosis of asthma of any severity and exclusion of alternative diagnoses, and at least 1 one the following, tested sequentially at screening or based on historical documentation :
- Bronchodilator reversibility after inhalation of SABA at screening or documented within the previous 24 months defined as an increase in FEV1 >= 12% and at least 200 mL from baseline. If reversibility is < 12 % and per the opinion of the PI, a repeat bronchodilator reversibility test is performed; this result may be used for subject ernollment.
- PC20 methacholine * 16 mg/mL at screening or documented within 24 months prior to screening.
- Obstructive physiology defined as a FEV1/FVC ratio < 0.7.
• Fall into 1 of the categories for asthma severity (mild, moderate, or severe) as described in

the study population (see Section 4.1).
• Prebronchodilator FEV1 **50% predicted at screening.
• Must have clinically stable asthma (see Section 7.2.2) for at least 6 weeks prior to screening.
• No acute illness including asthma exacerbation requiring augmentation of therapy in the 6 weeks prior to screening.
• Have been on their current asthma controller therapy for at least 6 weeks prior to screening. Mild asthmatics must have been off asthma controller therapy for at least 6 weeks prior to screening. Addition or withdrawal of asthma controller medications in order to be considered for participation in the study is prohibited.
• For asthmatic subjects participating in bronchoscopy:
- Must be between 18 and 55 years of age, inclusive, at informed consent.
- Must be judged by the PI to be a subject suitable to undergo bronchoscopy.
- No lifetime medical history of life-threatening asthma including intubation and ICU admission.
- Post-bronchodilator FEV1 * 60% predicted at screening.
- No history of adverse events associated with a prior bronchoscopy, including but not limited to, significant worsening of asthma, significant bleeding or reaction to sedative agents.
- No history of bleeding disorder including use of anticoagulants and antiplatelet agents that could place the subjects at risk of bleeding. Able to abstain from aspirin use for 7 days and NSAID use for 3 days prior to bronchoscopy without risk.
- No contraindications to conscious sedation or medications used in the bronchoscopy procedure.
• To participate in the optional genomic component of this study, subjects must have signed the informed consent for genomic research indicating willingness to participate in the genomic component of the study. Refusal to give consent for this component does not exclude a subject from participation in the study.

Exclusion criteria

Healthy Subjects
Exclusion Criteria
Subjects who meet any of the following criteria will be excluded from participating in the study:
• Be considered, in the opinion of the investigator, to be an unsuitable candidate for the study.
• History of any clinically significant medical illness or medical disorders including (but not limited to) cardiovascular disease, neuromuscular, hematological disease including bleeding disorders, respiratory disease, hepatic or gastrointestinal (GI) disease, neurological or psychiatric disease, ophthalmological disorders, neoplastic disease, renal or urinary tract diseases, or dermatological disease.
• Diagnosis of chronic obstructive pulmonary disease (COPD), cystic fibrosis, or other significant respiratory disorder including significant occupational or environmental exposures with ongoing respiratory symptoms.
• Have a bronchodilator response of more or equal to 12% and at least 200 mL from baseline

or an FEV1 value less than*85% of predicted value at screening.
• A known history of sleep apnea requiring medical intervention.
• Major or traumatic surgery within the 3 months prior to screening.
• Have a positive urine pregnancy screening result.
• Have a recent history (within previous 6 months) of alcohol or drug abuse.
• Positive urine toxicology screen for substances of abuse, including but not limited to cannabinoids, cocaine, and methadone
. Positive urine toxicology screen, including but not limited to amphetamines, barbiturates, benzodiazepines, opiates and tricyclic antidepressants. unless the results can be reliably attributed to a concomitant prescription medication by the PI for a condition identified on medical history, in which case the subject may be enrolled after consultation with and agreement of the spnsors medical monitor
• Have a positive urine screen for nicotine (urine cotinine test).
• Have a positive breath test for alcohol at initial screening visit.
• Have a positive serology test for HIV antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV) at screening.
• Have a positive Phadiatop test.
• Donated blood (volume >= *500 mL) within 56 days prior to screening.
• Received an experimental antibody or biologic therapy within the 6 months prior to screening, or received any other experimental therapy or new investigational agent within 60 days or 5 half-lives (whichever is longer) of study start.
• Be unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
• Is an employee or employee family member of the investigator, study center, or Sponsor.
• Any condition that, in the opinion of the investigator, would complicate or compromise the study, or the well-being of the subject.;Subjects with Asthma
Exclusion Criteria
• Be considered, in the opinion of the investigator, to be an unsuitable candidate for the study.
• History of any clinically significant medical illness or medical disorders that place the subject at risk from participation by the judgment of the PI including (but not limited to) cardiovascular disease, neuromuscular, hematological disease including bleeding disorders, respiratory disease, hepatic or GI disease, neurological or psychiatric disease, ophthalmological disorders, neoplastic disease, renal or urinary tract diseases, or dermatological disease. Subjects with stable, well-controlled conditions may be eligible after consultation with the Sponsor*s medical monitor.
• Diagnosis of allergic bronchopulmonary aspergillosis (ABPA), allergic bronchopulmonary mycosis (ABPM), or occupational asthma.
• Diagnosis of COPD, cystic fibrosis, or other significant respiratory disorder including significant occupational or environmental exposures with ongoing respiratory symptoms.
. If a PC20 mehacholine test is performed during screening for enrollment, a PC 20 result > 16 mg/ml excludes the subject from the study
• Major or traumatic surgery within 12 weeks of screening.
• A known history of sleep apnea requiring medical intervention.
• Have a positive urine pregnancy screening result.
• Have a recent history (within previous 6 months) of alcohol or drug abuse.
• Positive urine toxicology screen for substances of abuse, including but not limited to

amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates and tricyclic antidepressants.
• Have a positive urine screen for nicotine (urine cotinine test).
• Have a positive breath test for alcohol at initial screening.
• Have a positive serology test for HIV antibodies, HBsAg, or anti-HCV at screening.
• Donated blood (volume >= *500 mL) within 56 days prior to screening.
• Be unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
• Received an experimental antibody or biologic therapy within the 6 months prior to screening, or received any other experimental therapy or new investigational agent within 60 days or 5 half-lives (whichever is longer) of study start.
• Is an employee or employee family member of the investigator, study center, or Sponsor.
• Any condition that, in the opinion of the investigator, would complicate or compromise the study, or the well-being of the subject.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-07-2011
Enrollment:	34
Type:	Actual

Ethics review

Approved WMO

Date:	14-06-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL34963.078.10