Fluctuaties over de tijd van biomarkers bij patiënten met astma en gezonde controles; " proof of concept" voor het voorspellen van verlies van astma controle.

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1. Temporal fluctuation analysis of inflammatory biomarkers and clinical data enables individual risk assessment for loss of asthma control and asthma exacerbations. 2. The fluctuations in these biological parameters (biomarkers) change after...

Ethische beoordeling	Niet van toepassing
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON23727

Bron
Nationaal Trial Register

Verkorte titel
BIOFLUC

Aandoening

The health condition studied will be asthma, the participants will be monitored during stable episodes and will subsequently undergo nasal inoculation with Rhinovirus for inducing loss of control/mild exacerbation.

Ondersteuning

Primaire sponsor: Academic Medical Centre, Amsterdam
Overige ondersteuning: European Union, Marie Curie Program

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Clinical markers and biomarkers of inflammatory origin from blood, exhaled breath, nasal lavage and urine. These include:
• Lung function assessments such as Peak flow, Spirometry, Forced Oscillation Technique (FOT) and Fraction Exhaled Nitric Oxide that can be directly measured from the cases and the control subjects.
• Biomarkers of eosinophilic and neutrophilic inflammation (peripheral blood counts, Eosinophil Cationic Protein: ECP, Myeloperoxidase: MPO), related chemokines and interleukins (IL-5, eotaxin, IL-8, etc.) that can be assayed in blood/Nasal Lavage (NAL).
• Inflammatory low molecular weight compounds like bromo tyrosine, F2 isoprostanes, and lipid mediators like prostaglandins that can be analysed in exhaled breath/urine.
• Exhaled Volatile Organic Compound (VOC) metabolomics profiles measured by GC-MS and SpiroNose that can be helpful in distinguishing asthmatics from healthy subjects and discriminating inflammatory phenotypes of asthma.
• Inflammatory low molecular weight compounds, e.g. adenosines, nitro-tyrosines, malondialdehyde and others that can adequately be assessed in exhaled breath.

Toelichting onderzoek

Achtergrond van het onderzoek

SUMMARY

Rationale: Loss of control and exacerbations are a major burden for patients with asthma. Discriminating stable and unstable episodes in asthma is clinically relevant and imperative in individuals with risk of severe exacerbations. To that end, robust biomarkers indicating disease severity and control over time are necessary for predicting the severity of episodic exacerbations in asthma. Recent studies by the authors have shown that statistical time series modelling of clinical and physiological parameters capture information on diagnosis and control of asthma.

Hypothesis: We hypothesize that temporal fluctuation analysis of inflammatory biomarkers and clinical data enables individual risk assessment for loss of asthma control and asthma exacerbations.

Aim: To validate and compare the temporal behavior of a spectrum of biological and clinical non-invasive disease markers in asthma as compared to controls and use these time-series for predicting the risk/severity of rhinovirus-induced exacerbations for individual patients based on the multivariate model.

Objectives:
1. To investigate how temporal fluctuations of clinical and inflammatory biomarkers differ between patients with asthma and healthy controls.

2. To investigate how the fluctuations in these biomarkers change after experimental rhinovirus infection.

3. To use the time series and fluctuation analysis of these time varying biological and clinical parameters for the prediction of clinical severity of loss of asthma control/exacerbation as induced by rhinovirus

Study design:
The study begins with a screening visit followed by a 2 week run-in phase where the subjects will become acquainted with respect to all study measurements. The subjects will perform daily home measurements. At baseline again all study-measurements will be conducted.
The study will have two phases. Phase 1: A two-group observational prospective follow-up study, including patients with asthma and healthy controls during 50 days. Phase 2: A two-group prospective intervention study during 25 days, using inoculation with the common cold virus Rhinovirus 16. During phase 1, a predefined set of biomarkers will repeatedly be assayed in 12 controls and 12 patients with mild asthma. During phase 2, these subjects will undergo experimental rhinovirus infection to induce instability and potential loss of control/exacerbation. Temporal fluctuations of different biomarkers from various biological matrices screened would be used to predict for future risk analysis.
At the end all study parameters will be measured before terminating the study.

Study population: Patients with mild asthma who fulfil the criteria and healthy subjects aged between 18-50 years (for both the groups).
Main study parameters: Biomarkers of inflammatory origin from blood, exhaled breath, nasal lavage and urine. These include:

• Lung function assessments such as Peak flow, Spirometry, Forced Oscillation Technique (FOT) and Fraction Exhaled Nitric Oxide that can be directly measured from the cases and the control subjects.

• Biomarkers of eosinophilic and neutrophilic inflammation (peripheral blood counts, Eosinophil Cationic Protein: ECP, Myeloperoxidase: MPO), related chemokines and interleukins (IL-5, eotaxin, IL-8, etc.) that can be assayed in blood/Nasal Lavage (NAL).

• Inflammatory low molecular weight compounds like bromo tyrosine, F2 isoprostanes, and

lipid mediators like prostaglandins that can be analysed in exhaled breath/urine.

• Exhaled Volatile Organic Compound (VOC) metabolomics profiles measured by GC-MS and SpiroNose that can be helpful in distinguishing asthmatics from healthy subjects and discriminating inflammatory phenotypes of asthma.

• Inflammatory low molecular weight compounds, e.g. adenosines, nitro-tyrosines, malondialdehyde and others that can adequately be assessed in exhaled breath.

Main study endpoints are descriptive statistical outcomes:

• Mean, Covariance, Skewness, Autocorrelation, Cross correlation etc. between different biomarkers and symptoms for about 10 days initially during the stable phase and subsequently prior and post virus challenge.

• Approx Entropy, Autocorrelation, Crosscorrelations, Lyapunov exponents, Hilbert-Huang Transformation followed by De-trended Fluctuation Analysis will be done on the time series data of biological markers.

• Recurrence Quantification analysis to examine the correlation and recurrence pattern of fluctuations, if the data points are large enough to calculate embedding dimension and reconstruction delay.

• Finally a multivariate probabilistic prediction model using the correlation exponent values for risk prediction.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The study requires a high number of visits. Therefore, patients will be recruited by advertisement. The current outcomes have been chosen because of their non- or limited invasiveness. Rhinovirus-inoculation in healthy and asthmatic subjects has been standardized and safely performed and published by others and ourselves. The patients will be strictly monitored and a team of qualified pulmonologists will be available when needed.

Doel van het onderzoek

1. Temporal fluctuation analysis of inflammatory biomarkers and clinical data enables individual risk assessment for loss of asthma control and asthma exacerbations.

2. The fluctuations in these biological parameters (biomarkers) change after rhinovirus challenge.

3. Fluctuation analyses of time series of biomarkers could help us predict the rates of exacerbation risk, preventing hospitalizations and morbidity.

Onderzoeksopzet

The study starts with a screening visit followed by a run-in phase.

Then Phase 1 follows with baseline (day 0) and continues till the 49th day when these participants are exposed to RV16.

Then the phase 2 begins and ends on 74th day.

Onderzoeksproduct en/of interventie

Nasal inoculation with GMP Rhinovirus 16

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Asthma patients will be selected using the following inclusion criteria:
• Age 18-50 years

• History of episodic chest tightness and wheezing

• Intermittent or mild to moderate persistent asthma according to the criteria by the Global Initiative for Asthma (Global Initiative of Asthma. www.ginasthma.org)

• Non-smoking or stopped smoking more than 12 months ago and 5 pack years or less

• Clinically stable, no exacerbations within last six weeks prior to study

• Steroid-naïve or those participants who are currently not on corticosteroids and have not taken any corticosteroids by any dosing-routes within 6 weeks prior to the study or only using on-demand reliever therapy

• Baseline pre-bronchodilator FEV1 ≥ 70% of predicted

• Airway hyperresponsiveness, indicated by a positive methacholine bromide (MeBr) challenge test with PC20<= 9.8 mg/ml

• Positive skin prick test (SPT) to one or more of the 12 common aeroallergen extracts, defined as a wheal with an average diameter of => 3 mm

• No other clinically significant abnormality on history and clinical examination

• Able to give written and dated informed consent prior to any study-specific procedures

Healthy subjects will be selected using the following inclusion criteria

• Age 18-50 years

• Non-smoking or stopped smoking more than 12 months ago and 5 pack years or less Steroid-naïve, non-atopic participants who are currently not on any maintenance (subjects using oral contraceptives can be accepted)

• No maintenance medication

• Baseline FEV1 ≥ 80% of predicted

• Negative methacholine bromide (MeBr) challenge or PC20 ≥ 19.6 mg/ml

• Negative skin prick test (SPT) to all of the 12 common aeroallergen extracts

• Negative history of pulmonary and any other relevant disease

• Able to give written and dated informed consent prior to any study-specific procedure

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Potential subjects who meet any of the following criteria will be excluded from participation in the study:
• Women who are pregnant, lactating or have a positive urine pregnancy test at baseline visit
• Participation in any clinical investigational drug treatment protocol within the preceding 5 half-lives of the drug (or 12 weeks if the half life is unknown) before the screening visit
• Concomitant disease or condition which could interfere with the conduct of the study, or for which the treatment might interfere with the conduct of the study, or which would, in the opinion of the investigator, pose an unacceptable risk to the patient

Furthermore the following additional exclusion criteria will be used in part 2 of the study:
• RV16 titre > 1:8 in serum, measured at screening (visit 1) and also at Rhinovirus inoculation visit
• History of clinical significant hypotensive episodes or symptoms of fainting, dizziness, or light-headedness
• History of an asthma exacerbation within the last 6 weeks prior to the study
• Has had any acute illness, including a common cold, within 4 weeks prior to visit 1
• Close contact with young children or with any immunosuppressed patients
• Has donated blood or has had a blood loss of more than 450 mL within 60 days prior to screening visit 1 or plans to donate blood during the study.
• Positive for any virus in nasal lavage at Rhinovirus inoculation day

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-10-2015
Aantal proefpersonen:	24
Type:	Verwachte startdatum

Ethische beoordeling

Niet van toepassing

Soort:	Niet van toepassing

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 44025
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL5317
NTR-old	NTR5426
CCMO	NL54293.018.15
OMON	NL-OMON44025

Resultaten

Samenvatting resultaten
Muskulus M, Slats AM, Sterk PJ, Verduyn-Lunel S. Fluctuations and determinism of respiratory

impedance in asthma and chronic obstructive pulmonary disease. J Appl Physiol (1985) 2010; 109:1582-91.

Frey U, Brodbeck T, Majumdar A, Taylor DR, Town GI, Silverman M, et al. Risk of severe asthma episodes predicted from fluctuation analysis of airway function. Nature 2005; 438:667-70.

Sinha A, Yadav AK, Chakraborty S, Kabra SK, Lodha R, Kumar M, et al. Exosome-enclosed microRNAs in exhaled breath hold potential for biomarker discovery in patients with pulmonary diseases. J Allergy Clin Immunol 2013; 132:219-22.