The role of indoleamine 2,3-dioxygenase in virus-induced asthma exacerbations

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

Summary

ID

NL-OMON33934

Source
ToetsingOnline

Brief title
IDO and virus-induced asthma exacerbations

Condition

- Allergic conditions
- Viral infectious disorders
- Bronchial disorders (excl neoplasms)

Synonym
asthma, virus-induced asthma exacerbation

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Nederlands Astma Fonds

Intervention

Keyword: apoptosis, asthma, inflammation, virus

Outcome measures

Primary outcome

With this project we will analyze the expression (mRNA and protein) and activity (tryptophan and kynurenine in serum and BALF) of indoleamine 2,3-dioxygenase. In addition we will determine cell counts and phenotype of inflammatory cells in BALF, viral load and inflammatory mediator production in epithelial cells and BALF and apoptosis markers in BALF cells and airway epithelial cells. Endogenous standards will be used to compare between healthy indiviuals and allergic asthma patients and between the two different time-points (pre- and post-RV16 exposure). Regression analysis will be performed to link these parameters to clinical details (FEV1, PC20histamine, symptom scores for asthma and common colds).

Secondary outcome

There are no secondary study parameters

Study description

Background summary

Virus-induced exacerbations and the concomitant enhanced inflammatory responses present the major clinical manifestation of asthma but is poorly understood from a mechanistic point of view. This hampers the development of adequate prophylaxis and treatment of asthma exacerbations. Recent ex vivo studies have implicated a defective interferon (IFN)-beta and IFN-lambda production by airway epithelial cells and BALF cells in response to rhinovirus (RV) infection resulting in deficient apoptosis of virus-infected cells in asthma. There is as yet no in vivo data corroborating these findings, nor is known by which

mechamism apoptosis is induced. Indoleamine 2,3-dioxygenase (IDO) is a key anti-viral protein. In vitro and in vivo studies have revealed that IDO expression limits viral replication and inflammatory responses by promoting apoptosis of virus-infected cells and inflammatory cells (T cells and granulocytes), respectively. Interestingly, IDO expression is induced by Th1 cytokines (IFN-gamma) and reduced by Th2 cytokines (IL-4). As Th2 cytokines are relatively over-represented in airways of patients with asthma, we hypothesize that virus-induced IDO expression is reduced relative to that in healthy individuals and therefore viral infection and the inflammatory response are resolved to a lesser degree in asthma.

Study objective

With this project we aim to clarify the differences in airway pathophysiology between asthmatics and healthy controls that underlie the prolonged survival of virus and the exaggerated inflammation in virus-induced exacerbations of asthma. We will study apoptosis (acting as antiviral mechanism and as a mechanism resolving inflammation) in an experimental rhinovirus infection model in asthmatics and healthy controls in vivo.

Specific questions:
1) Is IDO expression and/or IDO activity impaired during rhinovirus infection in the airways of asthma patients versus healthy subjects and does it correlate with viral replication, T cell responses, eosinophil and neutrophil numbers and inflammatory mediator production?
2) Is rhinovirus infection in asthma patients associated with reduced apoptosis of airway epithelial cells, and of inflammatory cells, compared to that in healthy subjects?
3) Is IDO expression/activity is associated with clinical outcome after rhinovirus infection (asthma symptoms, spirometry, hyperresponsiveness)?

The answers to these specific question may help us to identify novel targets for therapeutic intervention.

Study design

Healthy individuals and intermittant to mild persistent allergic asthma patients will be experimentally infected with rhinovirus type 16 (RV16). The procedure of RV16 exposure will be performed at day 0. Two days prior to infection (day -2) the volunteers will undergo a bronchoscopy to obtain bronchoalveolar lavage fluid (BALF) and four epithelial brushes. The collected materials will be used to determine baseline levels of the primary study parameters. The bronchoscopy, including BALF and the epithelial brush, will be repeated on day 6 after RV16 exposure (RV16). In addition, lungfunctiontests (FEV1 and PC20histamine) will be performed on day 4 after RV16 exposure (baseline FEV1 and PC20histamine have been determined at the screeningsvisit).

Six weeks after RV16 exposure, blood will be drawn to confirm infection on basis of neutralizing antibodies.

Prior to this study we will perform a pilot study (5 patients in each group) using low-dose RV16, which was successfully used in a study-cohort of COPD patients. Based on the results of this pilot study, we will decide whether we use this low-dose RV16 or the normal RV16 dose that has successfully been used in previous studies with allergic asthma patients. Based on inflammatory mediator production in previous studies, we calculated that 14 individuals in each group is sufficient for our study. Anticipating on a drop-out rate of 15%, we need to include 16 individuals per group. We therefore need to recruit 5 (pilot study) + 16 individuals = 21 individuals per group.

Study burden and risks

After anamnesis and a physical examination, individuals will be subjected to a lungfunction test, 10 ml of blood will be drawn and a skin-prick test will be performed, which are considered to be a mild burden. Bronchoscopy, used to obtain BAL fluid and epithelial brushes, is an invasive technique that, despite the use of the anaesthetic lidocain, inflicts an unpleasant feeling and thus a considerable burden to the individual. A bronchoscopy may give rise to a dry cough and some distress to the nose, where the bronchoscope is inserted. During brushing a superficial bleeding may develop which normally stops rapidly. The bronchoscopy will take about 15 minutes to complete.

Experimental RV16 infections will cause mild commom-cold symptoms in both healthy individuals and stable allergic asthma patients. RV16 infection will evoke a transient exacerbation of asthma symptoms. The RV16 infection protocol is a standard procedure to challenge healthy individuals, intermittent and mild persistent (allergic) asthmatics and COPD patients. The rationale for using RV16 is that this rhinovirus strain causes mild common-cold symptoms as compared to other rhinovirus strains. In addition, rhinoviruses are endemic, causing common colds in the general population. No adverse events of using RV16 inoculation in healthy indivuals and patients (asthma and COPD) have been reported. Exposure to RV16 will cause considerable burden that will last for several days (up to a week).

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

Inclusion criteria for allergic asthma patients:
- Controlled, intermittant to mild persistant asthma patients (according to the updated (2007) GINA guidelines);
- FEV1 at baseline at least 80% of the predicted value;
- baseline bronchial hyperresponsiveness to histamine (PC20histamine) between 0.25 and 8 mg/ml;
- Skin-prick test positive to common allergens;
- Patients are treated with inhaled beta-2-agonists on demand only (twice a week or less);
- Age between 18 and 40 years;;Inclusion citeria for healthy subjects:
- FEV1 at baseline at least 80% of the predicted value and baseline;
- PC20histamine above 16 mg/ml;
- Skin-prick test negative to common allergens;
- Age between 18 and 40 years;

Exclusion criteria

Exclusion criteria for allergic asthma patients:
- Moderate to severe asthma patients (according to the updated (2007) GINA guidelines);
- Allergic asthma patients with daily symptoms;

- Nocturnal symptoms more than once a week;
- Patients who have had an exacerbation during the past 6 months, as indicated by a course of systemic steroids or antibiotics;
- Patients that used (inhaled) steroids less than 6 weeks prior to the study;
- Smokers;
- Ex-smokers (< 12 months or > 5 packyears);
- Circulating antibodies against rhinovirus type 16;
- Patients who are in close contact with young children (< 2 years), either professional or family related.;Exclusion criteria for healthy subjects:
- Healthy subjects with a history of pulmonary complaints;
- Smokers;
- Ex-smokers (< 12 months or > 5 packyears);
- Circulating antibodies against rhinovirus type 16;
- Patients who are in close contact with young children (< 2 years), either professional or family related.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2008
Enrollment:	42
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL21836.018.08