Infection prevention and immune modulation by bacterial lysates in patients with asthma: gaining insight into the mechanism of an old therapy

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To diminish the number of asthma exacerbations with the regular use of a bacterial lysate.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON43072

Source
ToetsingOnline

Brief title
BREATHE

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Bronchial disorders (excl neoplasms)

Synonym
asthma, reactive airway disease

Research involving
Human

Sponsors and support

Primary sponsor: Sint Franciscus Gasthuis
Source(s) of monetary or material Support: OM Pharma/ Vifor Pharma,Stichting

Coolsingel;OM Pharma;ESPID

Intervention

Keyword: asthma, immune modulation, infection prevention, respiratory tract infection

Outcome measures

Primary outcome

Number of astma exacerbations within 18 months after initiation of intervention.

Secondary outcome

Number of respiratory tract infections within 18 months after initiation of intervention, change in pulmonary function from baseline, use of antibiotics, oral corticosteroids and *2-agonists, quality of life, outpatient doctor*s visits and hospitalisation, adverse events, viral colonisation dynamics in time, bacterial colonisation dynamics in time, sputum and blood-inflammatory parameters (especially TH1/Th2 and ILC2) dynamics in time and during RTI.

Study description

Background summary

Respiratory tract infections (RTI) are responsible for a large morbidity, especially in patients with asthma. Asthma is caused by a complex interplay of genetic predispositions and environmental stimuli. Microorganisms often elicit exacerbations. Prevention of respiratory tract infections might therefore aid in controlling asthma symptoms. There are several methods aiming at prevention of respiratory tract infections, mainly being vaccinations (including their non-specific immunological effects, e.g. BCG-vaccine), maintenance antibiotics, probiotics and hygiene measurements. Oral polyvalent bacterial lysates recently gained renewed attention. These contain bacterial peptides derived from killed pathogenic respiratory bacteria and have been designed in the *70s. They act as immune-modulators and follow the route of the natural evoked immune response. In the intestine, they trigger the gut-associated lymphoid tissue (GALT) system

and modulate the immune system, leading to stimulation of dendritic cells with activation of B- and T-memory cells. Increased cellular and polyclonal humoral responses including selective IgA secretion, macrophage activation and secretion of pro-inflammatory cytokines have been observed in mouse models. This led to effectively boosted pathogen destruction with a decrease in severe viral and bacterial infections.
Bacterial lysates have been prescribed for years in many European countries to prevent RTI and have a long and safe record in adults and children. However, hardly any large and good quality clinical studies have been performed till now. Systematic reviews and meta-analyses showed (significantly) fewer RTI (20-40%) after bacterial lysate therapy. However, patients with comorbidity who might benefit most, such as asthma or mild immunodeficiency, were usually not included in these studies. In pre-school children with asthmatic symptoms, the number of RTI and wheeze episodes significantly diminished after using bacterial lysates. In older persons with COPD, bacterial lysates diminished respiratory symptoms and bacterial infections. No human studies looking at the microbiological and immunological phenomena in detail with new techniques have been performed yet.
Interestingly, bacterial lysates do not only upregulate the antimicrobial immune response, the Th1-response, but also seem to downregulate the Th2-response that is related to allergic diseases. The key inflammatory cell in this process is the regulatory T-cell (T-reg). 9 This cell has an important role in maintenance of immunological homeostasis in the body. In an asthmatic mouse model, significantly lower numbers of inflammatory cells were found after administering bacterial lysates. Th2-type cytokine levels were diminished and expansion of Treg-cells was observed. 10
Recently, innate lymphoid cells group 2 (ILC2) were discovered and these cells have been related with asthmatic symptoms following viral respiratory tract infection. Induction of ILC2 directly by viruses has been associated with airway inflammation and hyperreactivity by production of type 2 interleukins. The effect of bacterial lysates on ILC2-activity (either or not related to activity on Treg-cells) is unknown.
Concluded, treatment by bacterial lysates seems to be promising therapy for preventing respiratory infections but lacks robust evidence. Even promising is its supposed modulation of the (asthmatic) inflammatory response by attenuation of Th2-related inflammation. This intervention study addresses the clinical effects of bacterial lysate therapy in a prospective controlled manner, combined with laboratory research into the development of microbial colonization and immunological aspects related to viral infections and inflammation.

Study objective

To diminish the number of asthma exacerbations with the regular use of a bacterial lysate.

Study design

Investigator-initiated double-blind randomized controlled trial.

Study burden and risks

Broncho-Vaxom is a bacterial lysate that has been used for years in children and adults with recurrent respiratory tract infections. It has a favorable after profile. However, for study purposes, it was hardly studies in asthmatic individuals, till now only in young children. In older subjects with COPD, bacterial lysates have a positive effect on lung health. We want to investigate whether this positive effect on lung health can also be observed in asthmatic patients.
Burden is regarded as low; in winter season participants have to take a pill daily for 10 days every month. Three-monthly visits will be scheduled as much as possible together with regular doctor's visits. Venapunctures are taken as much as possible from adult participants.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients with proven asthma (airway responsiveness proven by reversibility and histamine PC20 < 8 mg/ml)) who have recurrent airway signs and symptoms despite optimal maintenance medication (medium/high dose inhalation corticosteroid and long-acting *2-agonist; GINA 4).;Specific inclusion criteria
- * 2 documented asthma exacerbations in the past winter season (see definition below)
- and Asthma Control Questionnaire (ACQ) > 1.5 despite maintenance medication

Exclusion criteria

- Other relevant respiratory conditions, e.g. OSAS, bronchiectasis
- Systemic immunological diseases
- Current smoking or past smoking 10 pack years
- Other untreated co-morbidity, such as gastro-esophageal reflux disease, ENT problems, psychological disorders
- Non-compliance to current medication or inhalation technique
- Communication difficulties
- Pregnancy or planned pregnancy within 2 years

Study design

Design

Study phase:	4
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-10-2016
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Broncho-Vaxom (OM-85 BV)
Generic name:	Broncho-Vaxom (OM-85 BV)

Ethics review

Approved WMO Date:	25-04-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 28868
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2016-001213-24-NL
CCMO	NL57294.101.16
OMON	NL-OMON28868

Study results

Date completed: 01-07-2020

Actual enrolment: 75

Summary results
Trial is onging in other countries