Randomized,double-blind,placebo-controlled study comparing formoterol-beclometason 12/200 mcg BID versus placebo to evaluate the improvement of coughing and quality of life in subjects with bronchiectasis.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON50523

Source
ToetsingOnline

Brief title
FORZA study

Condition

- Respiratory tract infections

Synonym
chronic inflammatory airways

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Chiesi Farmaceutici

Intervention

Keyword: bronchiectasis, coughing, inhalation corticosteroid, long acting beta 2 agonist

Outcome measures

Primary outcome

Leicester cough questionnaire

Secondary outcome

Quality of Life Bronchiectasis (QOL-B) questionnaire*s respiratory symptom

domain

pulmonary function (FEV1)

the frequency of exacerbation requiring an intervention with systemic

antibiotics (oral/intravenous [i.v.])

24 hour sputum production (in mL);

dyspnea score using mMRC (Modified Medical Research Council)

adverse events

Assessing the inflammatory respons by analysing blood and sputum

Study description

Background summary

Bronchiectasis (BE) is a chronic disorder of the bronchi and bronchioles. BE has been defined as a rare disease. It is characterized by permanent dilation involving a degenerative vicious cycle of microbial infection and persistent

inflammatory response with the release of immune mediators and microbial toxins.
Clinically, patients complain about a (productive) cough that can yield large volumes of mucopurulent sputum, next to dyspnoea. Coughing is the major symptom in BE. Furthermore, haemoptysis can occur, sometimes patients have pleuritic chest pain, and wheezing. Fatigue is a frequent complaint, and acute exacerbations of airway symptoms are common. This chronic disease poses a large burden for the patient and for society because of the morbidity that includes work absences, reduced physical performance, and social distress.

The reported prevalence is largely unknown, but commonly seen in regular pulmonary practise. BE is usually diagnosed in middle aged and elderly patients, more female than male are affected. The golden standard for diagnosis is the high-resolution computed tomography (HRCT) scans.
The causes of BE are numerous. One of the most common causes is a previous respiratory tract infection with adenovirus, measles, influenza, Bordetella Pertussis, Staphylococcus aureus, Mycobacterium tuberculosis, Streptococcus pneumonia, or other bacterial pathogens, resulting in lung damage. But up to 50 - 80% of cases of BE are considered to be of idiopathic origin. Hence, the etiology of BE can be categorized as idiopathic, post-infectious, or due to an underlying anatomic or systemic disease.

The management of BE requires treatment of the underlying cause and to prevent and treat recurrent infection. Currently, the management consists of bronchial hygiene either pharmacologically or mechanically, administration of courses of pathogen directed antibiotic treatment and maintenance treatment with macrolides to prevent new exacerbations. In real-life setting however, approximately 60% of BE patients in the EMBARC registry (https://www.bronchiectasis.eu) showed that they received a long acting bronchodilator (LABA) and almost as many were in receipt of an inhaled corticosteroid (ICS). Most of the pharmacotherapy are based on the empirical treatment for COPD or asthma. In patients with asthma or COPD, ICS and LABAs have proven to be beneficial for a subgroup of patients in terms of improvement of health-related quality of life and reduction of exacerbations.
In the management of BE, bronchodilator treatment and use of inhaled steroids is still a matter of debate, as only one long-term randomized parallel-group controlled trial has been performed. Martinez-Garcia published a prospective double blind study in which non-CF BE patients were randomised to either combined formoterol and medium dose budesonide (18/640mcg daily), or budesonide (1600mcg) alone by Turbuhaler. In the study, 40 patients were included and subsequently received budesonide (1600mcg daily) during 3 months in the run-in period. After randomisation they received either combination therapy or continued the budesonide for another 3 months observation period. 37 patients completed the study. The observations included HRQL, pulmonary function tests and microbiologic isolates. The study showed a clinically significant improvement in HRQL (symptom score domain) in the subgroup using combination therapy. No change was seen in exacerbations, nor in pulmonary function or

microbiologic cultures. The limitation of this study is the small sample size and the fact that it was a single centre study. Moreover there was no placebo control group in the study design, so all patients did receive an inhalation steroid. The question can be raised that the effect is merely through the LABA component. In addition the clinical relevant amount of sputum and purulence were not assessed in this study. In an observational study by Ping Wei et al, 120 patients were assigned to combined inhaled therapy (salmeterol-fluticasone, Seretide 250 microgram) versus routine therapy. The seretide group showed significant improvement in clinical symptoms and reduced exacerbation frequency. There was no improvement of pulmonary function.
Other clinical studies using salbutamol showed an improvement in pulmonary function in most cases of BE patients. British Thoracic Society guideline for Non-CF BE suggest that bronchodilator use may be appropriate for patients with bronchiectasis who have reversible airflow limitation.
The position of single use ICS in the treatment of Non-CF BE is still unclear. However some authors have claimed beneficial effects of ICS, such as improvement of the HRQL and a reduction in daily sputum volume. In the study by Tsang et al, 86 patients were randomized to receive either fluticasone 500 microgram twice daily or matched placebo. The authors only claimed effects on 24 hour sputum volume and exacerbation frequency. No effects were seen on pulmonary function tests.
However, in all described studies there was no clear exclusion of patients with Asthma or COPD. To determine the effect of ICS/LABA in BE; these patient groups have to be excluded, because of the known beneficial effects of ICS/LABA.
The current study will be the first study excluding patients with Asthma and COPD.

Study objective

Since coughing is the major symptom in BE, the objective of this trial is to evaluate the clinical efficacy of ICS/LABA treatment in subjects with BE on coughing. The primary outcome variables of interest is the Leicester cough questionnaire (LCQ), also we look at the improvement of health related quality of life (using the QOL-B questionnaire) and exacerbation frequency in a prospective setting. The use of the LCQ questionnaire in BE has been validated in other studies.

Study design

A prospective double-blind randomized controlled trial comparing Formoterol-beclomethasone 12/200 mcg BID versus placebo to evaluate the reduction in cough measured by the LCQ in patients with BE, excluding asthma COPD. And for the secondary objective the improvement of health-related quality of life and on symptoms and pulmonary function (FEV1) and the frequency of exacerbation requiring an intervention with systemic antibiotics (oral/intravenous [i.v.]) in subjects with non-CF BE.

Eligible subjects will be randomized to treatment with formoterol-beclomethasone or matching placebo.
All subjects will be treated with the regimen of medication for 3 months. An end-of-study (EOS) visit will be performed after completion of the follow-up period.

Intervention

Formoterol-beclomethasone 12/200 mcg BID versus placebo inhalation dosis aerosol for a period of 3 months

Study burden and risks

Benefit:
- reduction in coughing and therefore improvement in quality of life
- reduction in exacerbations

Risks:
- experience of Adverse events, like development of hoarseness; oral candidiasis; tachycardia
All adverse events are reversible after withdrawal of the medication. oral candidiasis will need topical treatment with good reaction

An inhalation with the medication will last 1 minute

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

· Age >= 18 years;
· Symptomatic patient (wheezing, cough and dyspnoea);
· Proven and documented diagnosis of BE by high resolution computed tomography
· Stable pulmonary status as indicated by FEV1 (percent of predicted) >=30%
· Stable clinically phase (ie, subjects free from acute exacerbation for at least 6 weeks prior to the start of the study);
· Stable regimen of standard treatment if used as chronic treatment for BE, at least for the past 4 weeks prior to screening. And/or macrolides if used as chronic treatment for BE at least for the past 6 months prior to screening;
· Coughing on the majority of days.

Exclusion criteria

Possible asthma according to the definition of the Global Initiative for Asthma (GINA) with:
o Positive bronchodilator reversibility test (increase in FEV1 of >12% and >200 mL from baseline, 10-15 minutes after 200-400 mcg salbutamol or equivalent)
OR
o Positive bronchial challenge test (fall in FEV1from baseline of >=20% with standard doses of methacholine or histamine)

- Known intolerance for ICS or LABA.
- Current ICS use
- Other cardiopulmonary conditions (other than bronchiectasis) that could modify spirometric valeus.
- Women who are pregnant, lactating, or in whom pregnancy cannot be excluded;
- Cigarette smoking history of > 10 pack-years and/or current smokers;
- Expected to die within 72 hours after enrolment

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-01-2019
Enrollment:	72
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fostair®
Generic name:	beclometasone/formoterol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	06-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-10-2018
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2022
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
EudraCT	EUCTR2017-001665-25-NL
CCMO	NL61630.078.18