Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma: The TASMA study

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AIMTo discover the molecular, cellular and structural airway targets of BT and link these to severe asthma phenotypes and outcome.OBJECTIVES1. To identify molecular and cellular targets of BT therapy and related changes in airway remodelling. 2. To...

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

Summary

ID

NL-OMON47504

Source
ToetsingOnline

Brief title
Targets of ThermoplAsty in Severe asthMA: TASMA-study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
asthma, asthmatic bronchitis, reversible airway obstruction

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMw,Boston Scientific,Longfonds;Boston Scientific

Intervention

Keyword: Airway smooth muscle, Asthma, Bronchial Thermoplasty, Optical Coherence Tomography

Outcome measures

Primary outcome

Primary endpoint is the difference in change in ASM mass as determined by the percentage of ASM surface area in airway biopsies between the immediate BT group and the delayed BT group = control group (n=20/group)

Secondary outcome

Secondary endpoints are BT-induced changes in:

1. ASM mass as determined by percentage/absolute ASM surface area or distance of reticular basement membrane (RBM) to ASM layer in endobronchial biopsies.

2. mucosal endobronchial biopsy and induced sputum inflammatory cell density/counts (eosinophils and neutrophils);

3. OCT- and rEBUS-determined changes in structural airway remodelling as measured by changes in lumen area (Ai) and airway wall thickness (Aaw) and composition (Figure 4);

4. Clinical outcome parameters including pulmonary function tests (pre-and post bronchodilator FEV1, PC20 methacholine (PC20 Meth), FeNO and airway-resistance (sRaw)/-compliance(sGaw)/-mechanics (FOT) parameters, asthma control questionnaire (ACQ), asthma related quality of life questionnaire (AQLQ), health care utilization (number of severe asthma exacerbations, emergency room visits, hospital and intensive care unit (ICU) admissions).

Statistical analyses performed on these secondary endpoints are:

A. comparative between BT treatment and control groups (n=20/group) if not a primary endpoint;

B. paired before and after BT analyses in all BT treated subjects (n=40) and;

C. comparative between BT-treated and untreated (right middle lobe RML) areas of the lung in all BT-treated subjects (n=40) if applicable for that endpoint:

Correlation/responder analyses between baseline factors and endpoints and predefined subgroup analyses.

Study description

Background summary

RATIONALE
Approximately 5% of asthma patients suffer from severe asthma that is characterized by frequent asthma exacerbations resulting in significant morbidity and excessive utilization of health care resources. Therefore, there is a strong need for improved therapeutic strategies for these patients. Insight in the pathogenesis and molecular pathways active in severe asthma is crucial to reach this goal. Bronchial Thermoplasty (BT) is a novel, innovative device-based treatment of severe asthma that is based on local, radiofrequent energy delivery in larger airways during bronchoscopy. Although proven effective on clinical outcomes in recent randomized trials, the mechanism that determines BT effective is largely unknown.

HYPOTHESIS
BT-induced clinical improvement in severe asthma is a consequence of reduction in airway smooth muscle (ASM) mass and (immunomodulatory) function, inflammation, neural innervation and/or vascular integrity resulting in altered airway remodelling. BT target identification and severe asthma phenotyping are critical for improved patient selection for BT and fundamental to discovering novel, specific signalling pathways active in severe asthma.

Study objective

AIM
To discover the molecular, cellular and structural airway targets of BT and link these to severe asthma phenotypes and outcome.

OBJECTIVES
1. To identify molecular and cellular targets of BT therapy and related changes in airway remodelling.
2. To link objective 1 to in vivo Optical Coherence Tomography (OCT)- and radial endobronchial ultrasound (rEBUS)-detected BT-induced changes in airway remodelling in severe asthma.
3. To phenotype and monitor severe asthma before and after BT by clinical parameters including induced sputum, bronchial hyper-responsiveness (BHR, PC20 methacoline), forced expiratory volume in 1 second (FEV1) and fractional exhaled nitric oxide (FeNO) and molecular parameters including RNA-derived transcriptomes extracted from severe asthma biopsies/brushes; results are compared to mild asthmatic and healthy controls.
Key Objective 1. and 2. will be linked to clinical outcome parameters.

Study design

The investigator-initiated TASMA trial aims to integrate the expertise of the AMC Amsterdam in severe asthma, basic research and lung physiology with the expertise in Interventional Pulmonology in AMC Amsterdam, UMCG Groningen, Thoraxklinik, Heidelberg, Germany and Royal Brompton, London, United Kingdom. This study recruits 40 severe asthma patients for BT at 4 sites in Europe (n=9-12/center: AMC, Amsterdam; UMCG, Groningen. Thoraxklinikum Heidelberg, Germany, Royal Brompton Hospital, London, United Kingdom). This number of patients is based on the previously described discriminative power of primary and secondary endpoints used for key objectives 1 to 3. Each site will enrol 9-12 patients, after the patient has been diagnosed with severe asthma, fulfilled in- and exclusion criteria and has provided informed consent to participate in the study. In- and exclusion criteria are described separately in *study population/enrolment and patient selection* in the protocol. Patients will be screened and phenotyped by demographic data, medical history, body mass index (BMI), atopy, routine blood analyses including blood eosinophils, induced sputum, chest X-ray, HR-CT of the chest, asthma control questionnaire (ACQ) and pulmonary function tests (spirometry including FEV1, body plethysmography, methacholine challenge test (PC20 Mch) and fractional exhaled nitric oxide (FeNO)).

The study has a two-armed, randomized design with immediate BT treatment in the first group and delayed BT treatment in the control group (n= 20 / group). This strategy will generate power for controlled (between group) BT target identification including ASM mass and clinical outcome analysis including PC20, FEV1, asthma symptoms/quality of life (ACQ, AQLQ) and health care utilization including frequency of emergency room visits, hospital admissions, severe asthma exacerbation frequency (secondary endpoints) with maximal power for paired analyses before and after BT (n =40).

After informed consent followed by standard BT screening patients will be randomized to an immediate and delayed BT-treatment group. The delayed BT group

serves first as a control group in between BT and control group analyses (n=20/group) and second to increase the sample size of active treatment in paired analyses before and after BT (n=40). Standard screening to determine a patient suitable for BT includes a single bronchoscopy for detection of gross airway abnormalities, high-resolution computer tomography of the chest (HR-CT) including expiration phase, sputum induction, standard pulmonary function and blood testing before BT. Standard BT will be performed using the Alair system (Boston Scientific, USA) and therefore patients will undergo 3 bronchoscopy procedures with BT at least 3 weeks apart within a 2 months period. Standard BT follow-up afterwards includes routine blood analysis, pulmonary function tests and HR-CT at 24 weeks. For research purposes, we ask patients to undergo a maximum of 2 extra bronchoscopies: 1 bronchoscopy in the immediate BT group (24 weeks after BT) or 2 bronchoscopy in the delayed BT group (3 weeks before and 24 weeks after BT). These bronchoscopies are on top of a single standard screening bronchoscopy before randomisation and BT during which airway sampling and OCT/rEBUS imaging is performed along with sputum induction, pulmonary function tests, questionnaires and venous blood sampling (see Table 1 and Figure 0.). Off protocol follow-up of patients will be offered by standard follow-up procedures yearly after BT treatment for 5 years.

Intervention

Bronchial Thermoplasty by the Alair system (Boston Scientific, USA). 1 (immediate BT group n=20) of 2 (delayed BT group n=20) additional bronchoscopies for airway-sampling and -imaging.

Study burden and risks

This study has a two-fold purpose: 1. to unravel the targets of BT in severe asthma (how does it work?) which is fundamental for better patient selection (who benefits most?) and further improvement of BT technology and novel asthma therapy development (how to treat better?). These objectives can only be achieved by linking patient-reported outcomes to airway structure/function, which is the principal aim of the study proposed. 2. to investigate clinical outcome analyses. These gaps in scientific knowledge and important questions are identified and articulated in the national and international severe asthma guidelines and need to be addressed for further application of BT in severe asthma. The proposed TASMA study is designed to fill these gaps and as such is critical for a broader application of this novel endoscopic treatment in severe asthma with possible lifelong benefit. The study protocol is judged methodologically Very Good (2x) or Excellent (4x) by six international experts. Two grants - Dutch Lung Foundation and ZonMw - are obtained to execute this study. The patient benefit of study participation is that he/she is offered a novel severe asthma treatment that is proven effective and safe with potential lifelong benefit but unfortunately not regularly available yet. For research purpose patients will be randomised to an immediate and delayed BT group

(n=20/group). The delayed BT group first serves as a control group and to increase the sample size of the active treatment group. For this reason we ask half of the patients to wait for 24 weeks for getting actual BT treatment. In addition we ask patients to undergo a maximum of 2 extra bronchoscopies: 1 bronchoscopy in the immediate BT group (24 weeks after BT) or 2 bronchoscopy in the delayed BT group (3 weeks before and 24 weeks after BT). These bronchoscopies are on top of a single standard screening bronchoscopy before randomisation and BT during which airway sampling and OCT/rEBUS imaging is performed along with sputum induction, pulmonary function tests, questionnaires and venous blood sampling (see Table 1 and Figure 0.). The bronchoscopies will be performed under conscious sedation (midazolam or propofol) to minimize patient discomfort. Previous experiences in research bronchoscopies in severe asthma patients by our group and others have proven these procedures to be safe. To our opinion the burden of either 1 or 2 additional bronchoscopies including airway sampling/imaging, sputum induction, pulmonary function test and questionnaires and postponing the actual BT treatment in half of the patients is justified by the scientific insights that can be obtained in this important trial in which a novel severe asthma treatment is offered that is otherwise not available.

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

symptomatic severe asthma despite optimal inhalation therapy
FEV1<= or >50% (stabilized on ICS/ABA) or post-bronchodilator FEV1 <= or > 60%
non-smokers

Exclusion criteria

age <18 or >65 years
other respiratory tract disease than asthma including bronchiectasis, infection
use of immunosuppressive therapy other than prednisolone <20mg/day
use of anticoagulants

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-04-2014
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	Bronchial Thermoplasty (Alair system)
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	17-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2017
Application type:	Amendment
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	NL45394.018.13