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Investigation of steroid responsiveness in patients with chronic obstructive pulmonary disease

Submission date
10/11/2016

Recruitment status
No longer recruiting

Registration date
15/11/2016

Overall study status
Completed

Last Edited
04/12/2024

Condition category
Respiratory

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease and currently a leading cause of chronic morbidity (long-term illness) and mortality (death). Inhaled corticosteroids (ICS) belong to the first line treatment for COPD patients; however, there are patients who do not get a significant clinical benefit from ICS. Additionally, ICS overuse results in considerable side effects and economic burden. The aim of this study is to investigate parameters that may help to identify COPD patients that respond better from patients that respond worse to treatment with ICS.

Who can participate?
COPD patients aged 40 and over

What does the study involve?
Participants undergo bronchoscopy, where an instrument called a bronchoscope is threaded through the nose and down the throat to examine the airways and take biopsies (tissue samples). Participants are then divided into two groups based on the area of airway smooth muscle cells (ASMCs). Group A includes patients with ASMC area over 20% and group B includes patients with ASMC area of 20% and lower. All patients are treated for 6 weeks with all three drugs: LAMA (aclidinium), LABA (formoterol) and ICS (budesonide). Patients from each group are then randomly allocated to receive either treatment with LAMA, LABA and ICS (groups A1 and B1) or treatment with LAMA, LABA and placebo (dummy drug) (groups A2 and B2) for 12 months. Participants are followed up at 3, 6, 9 and 12 months, undergo lung function and walking distance tests, and give blood samples and oropharyngeal (throat) swabs.

What are the possible benefits and risks of participating?
Participants receive all tests and treatments for free for the duration of the study (12 months). The risks of the study procedures are considered to be mild. The medication is licensed for use in COPD. Bronchoscopy is a routine test in patients with COPD and the risks of the procedure are minimal. Additional blood samples are taken at the start of the study, scheduled visits and COPD episodes. Oropharyngeal swabs are an established method to take samples and can cause mild

discomfort. All other procedures, including lung function and walking distance tests, are standard tests in COPD treatment. The side effects of inhaled steroids are usually mild, such as oral candidiasis (fungal infection in the mouth) and hoarseness. Patients are instructed at each visit how to avoid side effects (e.g. washing the mouth). The study team examine patients for any side effects.

Where is the study run from?
University Hospital Basel (Switzerland)

When is the study starting and how long is it expected to run for?
September 2016 to February 2020

Who is funding the study?
1. University Hospital Basel (Switzerland)
2. AstraZeneca (UK)

Who is the main contact?
Prof. Daiana Stolz
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
Histological, cellular and molecular investigation of steroid responsiveness in chronic obstructive pulmonary disease - the HISTORIC study

Acronym
HISTORIC

Study objectives
Chronic obstructive pulmonary disease (COPD) patients with increased airway smooth muscle cell (ASMC) area respond better to inhaled corticosteroids (ICS) and this type of histological analysis can predict steroid responsiveness in COPD patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
EKNZ (Ethikkommission Nordwest and Zentralschweiz), 12/12/2016, ref: 2016-01880

Study design
Investigator-initiated and -driven double-blind randomized placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied

Chronic obstructive pulmonary disease

Interventions
188 patients with COPD, GOLD groups B-D, are recruited within 18 months. Based on the histological analysis of endobronchial biopsies taken by flexible bronchoscopy, patients are divided into two groups. Group A includes patients with ASMC area >20% and group B includes patients with ASMC area ≤20%. All patients follow a run-in period of 6 weeks on open-label triple therapy with LAMA (aclidinium 400 mcg, bid), LABA (formoterol 12 mcg, bid) and ICS (budesonide 400 mcg, bid). Subsequently, patients from each group are randomized (1:1) to receive either:
1. Triple treatment with LAMA, LABA and ICS (groups A1 and B1) or
2. Combined bronchodilator therapy with LAMA and LABA and placebo for ICS (groups A2 and B2)
Randomization will be stratified by group (A vs B), follow a block size of 4. The duration of treatment will be 12 months, with follow-up at 3, 6, 9 and 12 months after randomization.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Budesonide, aclidinium, formoterol

Primary outcome measure
To compare the differences in the mean decrease of post-bronchodilator FEV1 in milliliters measured using a spirometer at 12 months, between patients with low (≤20%) and high (>20%) ASMC area and according to whether they received ICS or not

Secondary outcome measures
Immediately after the run-in phase, at 3, 6, 9 and 12 months after randomization to compare changes in:
1. Modified Medical Research Council (MMRC) dyspnea scale
2. COPD assessment test (CAT)
3. Health-related quality of life, measured using SF-36, SGRQ
4. Pre and post bronchodilator body plethysmography/DLCO
5. Expiratory FeNO
6. Single and multiple-breath N2 wash-out
7. Forced impulse oscillometry
8. 6-minute walking distance (6MWD)
9. Movement patterns, measured using accelerometry
10. Therapy-related side effects (oral candidiasis, tachycardia, tremor, hoarseness, pneumonia)
11. Exacerbations rate
12. Serum biomarkers
between patients with low (≤20%) and high (>20%) ASMC area and according to whether they received ICS or not

Overall study start date
01/09/2016

Completion date
30/04/2021

Eligibility

Key inclusion criteria
1. Age ≥40 years
2. COPD, as defined by the GOLD Guidelines and categorization in groups B-D
3. No acute exacerbation of COPD or any respiratory infection requiring medical attention or leading to a change in medication within the last 4 weeks
4. Unchanged respiratory medication regimen within the last 8 weeks
5. At least one exacerbation in the previous year
6. Current or ex-smokers with smoking history of ≥ 10 pack-years
7. Willingness to participate in a longitudinal, cohort study
8. Capability to provide written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
40 Years

Sex
Both

Target number of participants
64 patients with high ASCM and 88 patients with low ASCM should be included. Considering a 10% loss to follow up, the planned sample size is 188 patients

Total final enrolment
190

Key exclusion criteria
1. Rapid fatal disease (with life expectancy less than 3 months)
2. Pulmonary condition other than COPD as the main respiratory disease
3. Current diagnosis of bronchial asthma
4. Severe immune-suppression including HIV, organ transplantation, ongoing chemotherapy for cancer
5. Pregnancy or breastfeeding
6. Chronic use of oral steroids (> 10 mg per day) for COPD
7. Intolerance or contraindication to aclidinium, formoterol or budesonide

Date of first enrolment
01/03/2017

Date of final enrolment
31/03/2020

Locations

Countries of recruitment
Switzerland

Study participating centre
University Hospital Basel
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Sponsor information

Organisation
University Hospital Basel

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Sponsor type
Hospital/treatment centre

Website
http://www.unispital-basel.ch/das-universitaetsspital/bereiche/medizin/kliniken-institute-abteilungen/pneumologie/

ROR
https://ror.org/04k51q396

Funder(s)

Funder type
Hospital/treatment centre

Funder Name

University Hospital Basel

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The findings from this study are expected to be published in peer-reviewed journals. Criteria for authorship will be based on the rules of The Lancet. Authorship rights are based on active contribution to the study, including study design and planning, funding, patients' recruitment and follow-up, data collection, data analysis and manuscript preparation. Individual contributions and potential conflicts of interest will be specified. All publications containing study related data, e.g. scientific abstracts or manuscripts, shall be revised and approved by the steering committee before submission.

Intention to publish date
01/07/2023

Individual participant data (IPD) sharing plan
All relevant information regarding the datasets (including all analyses described in the primary and secondary outcome measures) are/will be available upon request from Prof. Daiana Stolz (Daiana.Stolz@usb.ch). Informed consent was obtained from all patients included in the study.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		20/07/2023	25/07/2023	Yes	No
Results article		19/04/2024	22/04/2024	Yes	No
Other publications		29/05/2024	30/05/2024	Yes	No