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A controlled clinical trial to evaluate a personalised treatment approach for the management of acute exacerbations (flare-ups) of chronic obstructive pulmonary disease (COPD)

Submission date
28/01/2019

Recruitment status
Suspended

Registration date
01/02/2019

Overall study status
Completed

Last Edited
03/04/2020

Condition category
Respiratory

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Chronic Obstructive Pulmonary Disease (COPD) is a burdensome, long-term lung disease causing persistent respiratory symptoms and narrowing of the airways. It affects over 10% of people aged over 40. Acute exacerbations of COPD (AECOPD) are symptom flare-ups which cause poor health, hospitalisation or death. They are responsible for 1 in 8 hospital admissions in the UK. While different AECOPD types require different treatments, there are no accurate tests to distinguish them. As a result, all AECOPD are treated the same, with inhaled relievers, to open-up the airways, steroid tablets to treat inflammation, and usually antibiotics to treat infections. However, antibiotics are beneficial only to half of all AECOPD that are caused by bacteria (bugs) and steroid tablets are only effective in 30-50% which are triggered by inflammation in the airways with eosinophils (a special type of white blood cells). Therefore, both steroids and antibiotics are overused, posing unnecessary risks to patients with COPD. For instance, steroids could cause infections or fractures, while antibiotics overuse can lead to the development of dangerous superbugs. Procalcitonin and eosinophils (EOS) are promising blood tests (biomarkers) that could target the use of antibiotics and steroids, respectively, and should be tested in a large clinical trial simulating real-life. This provides a potential opportunity to personalise the management of AECOPD, which could lead to improved use of healthcare resources and a reduction in the frequency of side effects and antibiotic burden (the development of superbugs). The aim of this study is to assess whether the combination of procalcitonin and EOS can identify moderate or severe AECOPD associated with bacterial infection or EOS airway inflammation, and can safely and effectively decrease and target the use of antibiotics and/or steroids. As this is the first study assessing this biomarker combination, only 135 participants are recruited to get an insight into the effects of the intervention and the information needed to launch a larger, confirmatory trial in the future.

Who can participate?
Patients aged over 40 with moderate or severe AECOPD

What does the study involve?
Participants are randomly allocated to receive antibiotic and/or oral steroid treatment guided by biomarkers, or standard courses of antibiotics and oral steroids. All participants receive bronchodilators (inhaled and/or nebulised).

What are the possible benefits and risks of participating?
Participants are assessed more closely for the duration of the study and their COPD treatment will be optimised by experienced members of the research team. In addition, the information collected from this study will help to improve treatment of COPD exacerbations in the future. The study will be the first to assess whether procalcitonin and blood eosinophil count can be used to guide the use of both antibiotics and oral steroids for COPD exacerbations. Therefore, a minority of participants might test negative for both tests and will receive neither antibiotics nor oral steroids. This has not been tested before and there is a risk that it might delay recovery from the exacerbation.

Where is the study run from?
1. Wythenshawe Hospital (lead centre) (UK)
2. Salford Royal Hospital (UK)

When is the study starting and how long is it expected to run for?
December 2018 to September 2021

Who is funding the study?
Boehringer Ingelheim

Who is the main contact?
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Contact information

Type(s)
Scientific

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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
CPMS 40057

Study information

Scientific Title
Characterisation and targeted TReatment of ACute Exacerbations of Chronic Obstructive Pulmonary Disease: the TRACE-COPD randomised controlled trial

Acronym
TRACE-COPD

Study objectives
The study hypothesis is that blood eosinophil count and procalcitonin could be used to identify acute exacerbations of chronic obstructive pulmonary diseaes caused by bacteria and those triggered by enhanced eosinophilic airway inflammation and guide the administration of both antibiotics and systemic steroids.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/11/2018, North West – Greater Manchester East Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, Tel: +44 (0)207 104 8009, Email: nrescommittee.northwest-gmeast@nhs.net), ref: 18/NW/0710

Study design
Randomised; Interventional; Design type: Treatment, Process of Care, Complex Intervention, Management of Care, Other

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic obstructive pulmonary disease

Interventions
For randomisation, the trialists will use randomisation lists independently developed by their in-house biostatisticians. Participants will be stratified according to the recruiting hospital and setting and will be allocated in a 2:1 ratio to the biomarkers or standard care arms. More specifically, the biostatisticians developed four separate lists (one for each hospital and setting), using block sizes of 9. Sequenctially numbered sealed opaque envelopes were created by administrative staff and treatment allocation will be concealed to patients and researchers contributing to recruitment, until informed consent has been obtained.

Biomarker-guided treatment arm:
A biomarker-guided targeted treatment protocol for AECOPD. Standard courses of antibiotics (doxycycline, 7 days) and/or oral steroids (prednisolone, 5 days) will only be administered for serum procalcitonin levels >0.25µg/L and/or EOS >2%, respectively.

Standard care arm:
Standard care per NICE guidelines. Standard courses of oral steroids (prednisolone, 5 days) will be administered to all severe exacerbations and to moderate AECOPD characterised by significantly increased breathlessness. Standard courses of antibiotics (doxycycline, 7 days) will be administered to AECOPD associated with a history of more purulent sputum, or clinical or radiographic signs of pneumonia.

All participants in both arms will receive bronchodilators (inhaled and/or nebulised).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Doxycycline, prednisolone

Primary outcome(s)

1. The proportion of patients receiving antibiotics for the index exacerbation, evaluated between day 14-21
2. The proportion of patients receiving systemic steroids for the index exacerbation, evaluated between day 14-21
3. Acceptability of the intervention (qualitative data collected throughout the study and during focus group meetings with participants), recruitment and consent rate (evaluated at baseline)

Key secondary outcome(s))
1. Treatment failure at day 14. Treatment failure will be defined as lack of treatment success, significant symptoms deterioration leading to unplanned healthcare utilisation, or the clinical need for administration of additional antibiotics and/or systemic corticosteroids, or death by day 14
2. Time-to-treatment success, evaluated at day 14-21. Treatment success will be defined as the first day of three consecutive days when the patient will have returned to his normal health state or the first of seven consecutive days in which the patient will only report minor increase in symptoms compared to baseline, without fever or altered sputum color
3. Re-exacerbation rate and re-hospitalisation rate at 6 months
4. Mortality during the index exacerbation (before treatment success, to be evaluated between day 14-21) and at 6 months
5. Adverse events and serious adverse events, evaluated at day 14
6. Increased length of admission or (re-)admission due to side effects to study medications, evaluated at day 14-21
7. Adherence to the intervention by clinicians and patients, evaluated at day 14-21
8. The proportion of patients testing negative to both biomarkers (evaluated at baseline) and the safety of the intervention in this subgroup [see secondary outcomes 1-4]
9. Sample size for a future confirmatory trial, evaluated at day 14-21
10. Feasibility and challenges of community recruitment of patients with acute exacerbations of COPD, evaluated at baseline
11. Resources required for a future, confirmatory trial, including clinic rooms, time investment in the progamme by the study clinicians, evaluated at 6 months
12. Researchers' and participants' feedback on the study experience, challenges in the conduction of the study and selected outcomes, collected throughout recruitment
13. Systemic and exhaled biomarkers in different clusters of COPD exacerbations (biomarkers collected in every face-to-face meeting for the duration of the trial)
14. Bacterial and viral presence and load in different AECOPD clusters (samples collected in every face-to-face meeting for the duration of the trial)

Completion date
30/09/2021

Eligibility

Key inclusion criteria
1. Males or females aged > 40 years
2. With a smoking history of at least 10 pack-years
3. A previous clinical diagnosis of COPD
4. Presenting with a moderate or severe AECOPD
5. Not having received antibiotics or systemic steroids during the preceding two weeks.
6. Capable of giving an informed consent
7. Subjects who are willing to allow his/her general practitioner, to be notified of their participation in the study.

8. The study will define severe exacerbations as those requiring hospitalisation, based on NICE criteria and moderate as those requiring antibiotics and/or systemic steroids, but not hospitalisation, according to the judgement of the responsible clinician who will be unaware of procalcitonin and EOS levels (following NICE guidelines)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Patients who have already received antibiotics or systemic steroids during the 2 weeks preceding recruitment/randomisation to the TRACE-COPD study
2. Those presenting with decompensated type 2 respiratory failure, requiring non-invasive ventilation and those admitted to the intensive care unit upon presentation
3. Patients with a primary diagnosis of pneumonia
4. Patients with a current diagnosis of asthma
5. Patients with known immunodeficiencies, cystic fibrosis, active tuberculosis, clinically significant bronchiectasis, those receiving long-term antibiotics and those with life expectancy of less than a year
6. People not able or keen to provide an informed consent for the study
7. Female participants who are pregnant or lactating
8. Patients diagnosed with medullary thyroid carcinoma (as this secretes procalcitonin)
9. Participants in active clinical trials of investigational medicinal products (IMP) or people who participated in clinical trials of IMP during the preceding 6 months. We will not recruit patients participating in any trial on COPD exacerbations
10. Patients with known allergy or sensitivity to doxycycline or prednisolone or an absolute contra-indication to their use
11. Patients in active clinical trials of investigational medicinal products (IMP) or people who participated in clinical trials of IMP during the preceding 6 months
12. Patients participating in any trial on COPD exacerbtaions

Date of first enrolment
12/02/2019

Date of final enrolment
20/09/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Wythenshawe Hospital (lead centre)
Manchester University NHS Foundation Trust
Southmoor Road
Manchester
United Kingdom
M23 9LT

Study participating centre
Salford Royal Hospital
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Stott Lane
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M6 8HD

Sponsor information

Organisation
Manchester University NHS Foundation Trust

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Industry

Funder Name
Boehringer Ingelheim

Alternative Name(s)
Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim International GmbH, BI, BIPI

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository, the COPD research team pages of the Centre for Respiratory and Allergy Research website (http://research.bmh.manchester.ac.uk/respiratoryandallergy/Research/COPD). All subjects participating in the TRACE-COPD study will be consented specifically for future sharing of anonymised study data. The trialists will facilitate sharing of fully anonymised data with other researchers who provide a methodologically sound proposal. The data will be available for 12 years, following a 3-year period of exclusivity, that will allow those contributing to make full use of the data. The datasets will include all clinical data collected for the TRACE-COPD trial, as well as the levels of all biomarkers that will be measured. Data will be available for 15 years. The data repository will have a Steering Committee comprising the Chief Investigator, the Head of the Division of Infection, Immunity and Respiratory Medicine, a Research and Development Manager and a Biostatistician. The Steering Committee will meet quarterly to consider applications for access to data.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No